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ABDOMINAL TUMOURS IN INFANTS AND CHILDREN*

BY

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If abdominal tumours in children were symptomatic more often than they are, diagnosis would be simple and indications for management clear. However, abdominal tumours are usually silent. Frequently they are discovered accidentally. They may well be diagnosed by chance in the systematic work-up for apparently unrelated symptoms, as, for example, in a child with a fever of unknown origin who has dullness to percussion at his left base on physical examination and in whom a chest film reveals not pneumonia but a retroperitoneal tumour.

When one speaks about abdominal tumours in children two major tumours come to mind, the embryoma of the kidney or Wilms' tumour and the neuroblastoma. These two tumours are thought of almost to the exclusion of others and perhaps rightly so. They are not only the most usual and the most dangerous to life, but are also amenable to treatment, if happily the diagnosis is made early.

Long experience with these killers of children leads one to a philosophy of tumour management. In America, at least, cancer is the No. 2 killer of children, exceeded only by accidents. Probably the same is more or less true in Britain although you do not seem to lead the frantic lives that we do and perhaps cancer is even more important as a cause of paediatric death than are accidents.

It is our firm belief that abdominal tumours present an urgency, if not an emergency situation in management. Several valid reasons might be cited in support of this belief but, for the sake of a teaching point, the naive explanation that we give is that in every tumour, such as Wilms', there is a day when metastases take place. Before this day extirpation of the primary tumour should result in a complete cure. After this day extirpation of the tumour has no effect on mortality and in all likelihood even the addition of X-ray therapy and chemotherapy to the surgeon's armamentarium probably alters the prognosis but little.

Another key-stone in the management of abdominal

tumours lies in ordering minimal investigations, not only because more are unnecessary, but also because the longer a child lies about the wards of the hospital, the more opportunity he has for his abdomen to be palpated by enthusiastic members of the house staff and by medical students.

The third point in our philosophical management of tumours is minimal trauma by palpation, whether this be pre-operatively or at the operating table. We attempt ligation of the blood supply to the tumour before handling it, if at all possible. This philosophy leads us to place an adhesive sign on the abdominal skin which says, 'Do not palpate this abdomen' as soon as we have made the diagnosis of an intra-abdominal mass, and commonly leads us to wide incisions of the thoraco-abdominal variety in order to approach an intra-abdominal or retroperitoneal mass without undue manipulation.

The differential diagnosis of intra-abdominal tumours is certainly important, even though the tumour must come out, because of differences in the life history of these two major malignant lesions, the Wilms' tumour and the neuroblastoma, and operative management dictated by these differences. The Wilms' tumour has a capsule and, if this is ruptured spontaneously or during the operative procedure, the prognosis is tantamount to eventual death. The pattern of metastases is to the lung fields and seldom to the regional nodes. The mortality is high, the best results being obtained in those clinics where the aforementioned philosophy is carried out and where prompt surgery is followed by adequate irradiation.

The neuroblastoma, on the other hand, is frequently non-encapsulated; its metastatic pattern is to the bones of the extremities, to the skull and retro-orbital areas. Growth by direct extension into adjacent organs is common, and the best mortality is not necessarily reported from those clinics that treat neuroblastomas as they do Wilms' tumours by X-ray treatment immediately after surgery. This tumour apparently has a unique ability to revert from a malignant to a benign form. Although we realize that little or nothing in the way

*Lecture delivered at the University of Liverpool in June, 1959.

of therapy may be associated with this course of events, our own experience leads us to believe that the best results have been in those patients who had a major surgical insult to their tumour.

The intravenous pyelogram is at all odds the key study in the differential diagnosis of these two tumours. Some of the films shown here are far superior to others insofar as visualization of the kidney is concerned. The reasons for this include not only a better dye substance being available today, but also the technique currently in use for giving the patient a carbonated beverage to drink immediately after injecting the dye intravenously in order that the carbon dioxide liberated from the beverage will fill the stomach, push the viscera out of the way, and show the dye secreted by the kidney through a large radiolucent gastric shadow of gas. Furthermore, we now reinforce the intravenous dose of dye by a second injection if there is no apparent dye secretion in the first film taken five minutes after the initial injection. Perhaps a review of some of the problems presented by patients may serve to illustrate both the commonplace and the bizarre.

Case Reports

Case 1. M.B. This 1½-year-old boy had been chronically ill for four months with weight loss, fever and diarrhoea. Physical examination revealed dullness at the right lower base of the lung field posteriorly. The liver was palpable 3 cm. below the costal margin and the spleen

was enlarged. The preliminary film of his abdomen showed a huge mass in the right upper quadrant with amorphous calcification. The intravenous urogram showed a typical displacement of the right kidney by a suprarenal mass. This is the usual textbook picture of a suprarenal neuroblastoma. It is classical in the position of the tumour, the displacement of the pelvi-caliceal system of the kidney and in the appearance of the calcium (Fig. 1).

Case 2. D.C. A 3½-year-old boy had a three to four-week history of intermittent fever, abdominal pain, leg pain, sore joints, weakness and weight loss. The diagnosis of rheumatic fever was considered before admission to hospital. In hospital a physical examination revealed a mass in the left upper quadrant and an intravenous urogram indicated in the five-minute film displacement of the ureter both in the anterior-posterior and oblique projections. Calcium was also seen in this lesion. It soon becomes apparent that the neuroblastoma can appear anywhere from the cervical region to the coccyx. The calcium pattern varies and is not 100% reliable. Here the tumour is not in the typical suprarenal position but is below the kidney (Fig. 2).

Case 3. E.B. A 23-month-old boy had intermittent episodes of diarrhoea for one year. More recently he had had an anaemia which had not responded to iron medication but he had not experienced fever or weight loss. On physical examination a palpable abdominal mass was found in the left flank. Intravenous urography revealed a displacement of the left ureter medially and anteriorly by a retroperitoneal mass lesion containing no calcium. This also proved to be a neuroblastoma (Fig. 3).

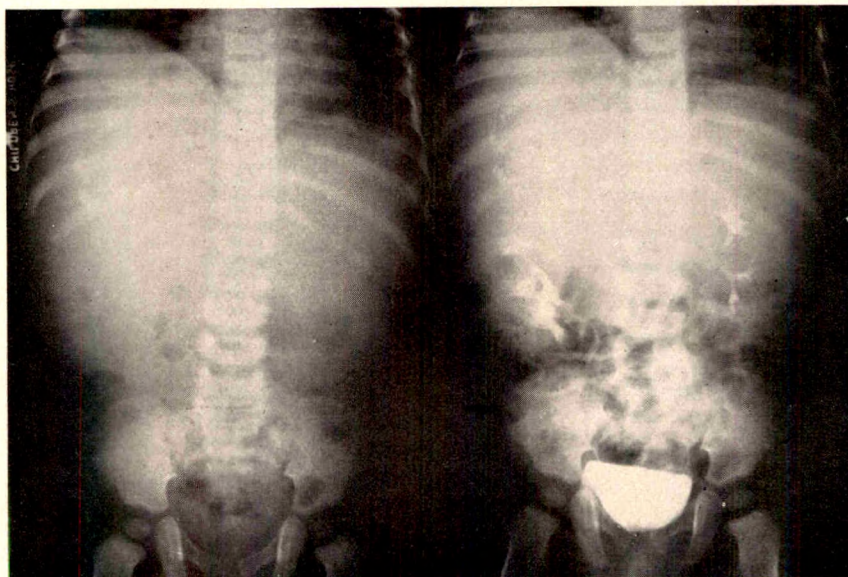


FIG. 1.—Case 1. Typical displacement of right kidney by a suprarenal neuroblastoma. Note calcific shadows.

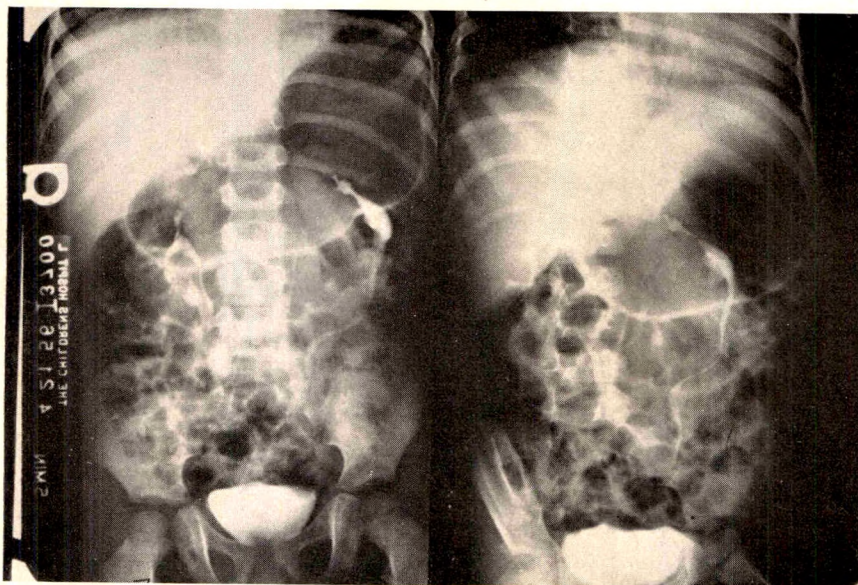


FIG. 2.—Case 2. Neuroblastoma. Left upper quadrant mass with displacement of ureter and kidney by infrarenal mass.

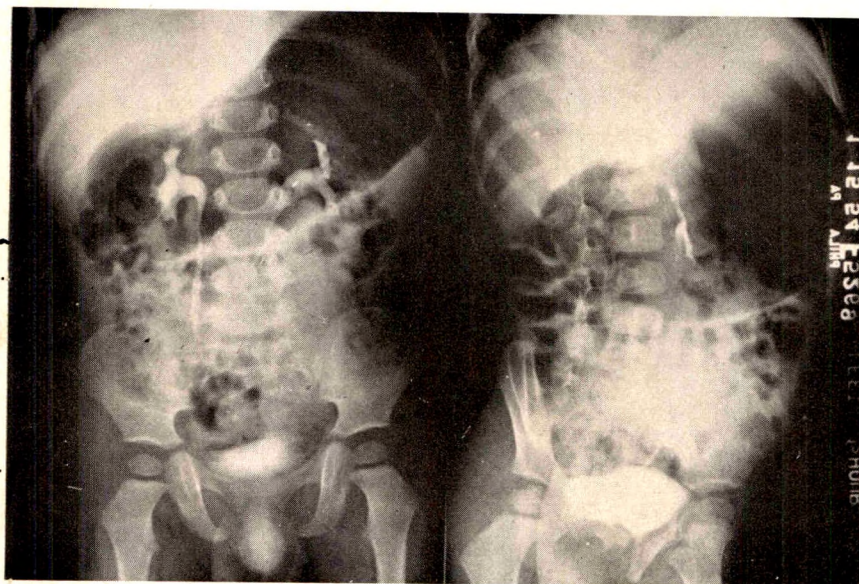


FIG. 3.—Case 3. Neuroblastoma. Left ureter displaced medially and anteriorly. No calcium.

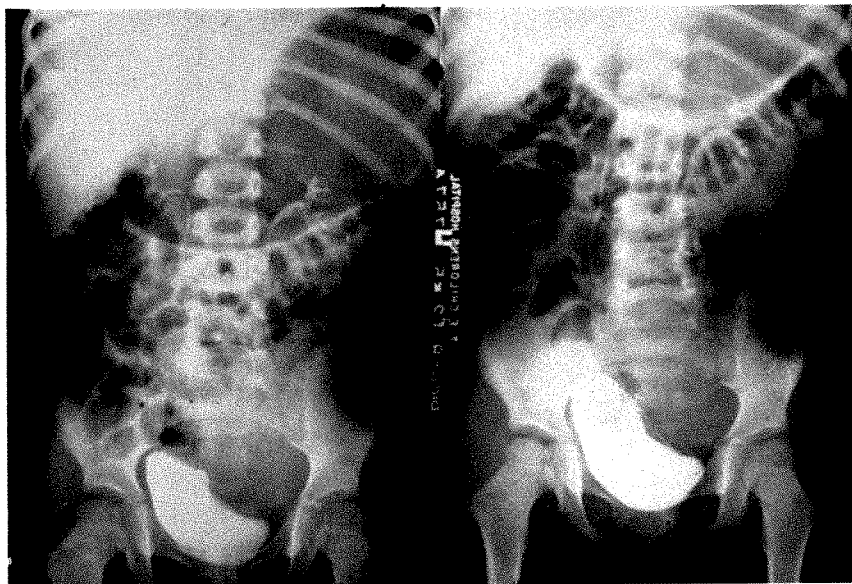


FIG. 4.—Case 4. Neuroblastoma. Mass indenting bladder and displacing ureter far laterally. Excellent demonstration of benefit derived from gas shadow in stomach produced by carbonated beverage.

Following extirpation of the tumour the child is alive and well four years post-operatively.

Case 4. S.C. A 3½-year-old girl had had poliomyelitis at the age of 4 months. One year before admission she began to complain of pain in her left leg and had numerous hospital admissions, all of which resulted in the assessment of her pain as a result of her poliomyelitis. By the time she reached the Children's Hospital of Philadelphia, the diagnosis was easy because there was a large mass not only palpable but also visible in her left lower quadrant. An intravenous pyelogram showed a mass indenting the bladder and displacing the ureter far laterally. This also proved to be neuroblastoma. The patient died six months later. The kidney is not displaced in any way in these films which show remarkably well the advantages of giving a carbonated drink in association with intravenous pyelography (Fig. 4).

Case 5. M.B. was a 5-year-old boy who entered the hospital with a four-month history of intermittent fever, pains in the joints, neck and head. At another hospital three months previously his long bones, intravenous pyelogram and skull films were all reported as being negative. By exclusion a diagnosis of Still's disease was made and he was placed on cortisone therapy. On this treatment he improved for a while but by the time of admission to the Children's Hospital of Philadelphia his pain had returned and his headaches were a primary symptom. Skull films showed evidence of increased intracranial pressure and a ventriculogram taken eight days later showed no mass lesion. A long bone survey done at the same time showed evidence of metastatic disease. Intravenous pyelography five days after the air

study revealed a neuroblastoma on the right side (Fig. 5). Everything about this patient was carried out in backward fashion. Diagnosis at the primary site was made only after metastases had appeared.

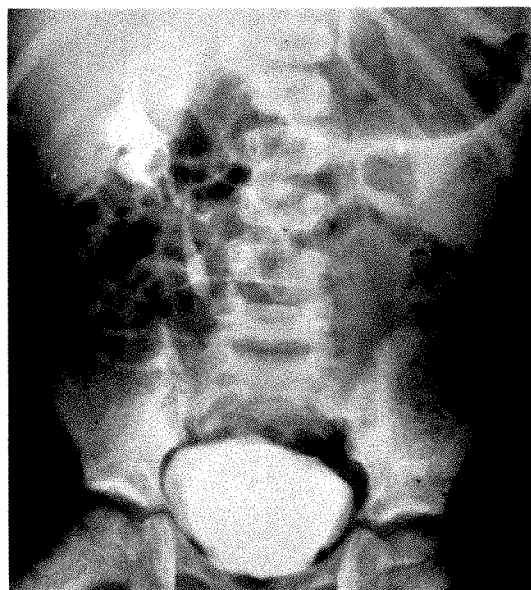


FIG. 5.—Case 5. Neuroblastoma on right. Diagnosis made only after metastases produced increased intracranial pressure.

In summary, concerning neuroblastomas, you have seen a textbook picture of the suprarenal position of a neuroblastoma above the kidney and a variation of the neuroblastoma below the kidney. One tumour displaced the ureter anteriorly and medially while still another displaced the ureter laterally and indented the bladder. Calcium was present in some but not in all flat films.

The histories of these patients included weight loss, pain, fever of unknown origin, diarrhoea and anaemia. In so far as similar syndromes are concerned, neuroblastoma mimicked poliomyelitis, arthritis and rheumatic fever. Such are the varieties of the neuroblastoma.

One of our residents married one of our nurses and in the course of time produced a child. By this time the young physician had moved to another city in the course of his training and when the child was born with an abdominal mass, the mass was assumed to be spleen because of a Rhesus incompatibility on the part of the parents. The mother took her baby into a rural area of Pennsylvania where the local physician watched the mass grow in size until it reached the umbilicus, whereupon the infant was referred to one of our medical confrères for evaluation of splenomegaly. It was obvious on examination of the abdomen that the mass in question was a retroperitoneal tumour and not spleen, and following the philosophy of management already outlined and spurred on additionally by the fact that the parents of the patient were our friends, the child was operated upon about six hours after admission to hospital. The tumour was a neuroblastoma and not only inoperable in the usual sense of the word by being wrapped around the hilum of both kidneys, but there were many metastases, multiple and small, covering the entire surface of the liver. Biopsy of both the primary and metastatic lesions showed an immature variety of neuroblastoma. Because of the helpless feeling of operating upon an impossible situation in a child of a friend, we attempted to scoop out what tumour we could, actually used very bad cancer surgical technique, and advised no X-ray therapy because we thought the child would not benefit from it and that the sooner he died the better for all concerned. Two weeks later his subcutaneous tissue was the site of multiple nodules such as one sees in a terminal leukaemia. To make a long story short, 13 years have gone by and this child is alive and well, has no abdominal tumour, even when his abdomen is palpated under anaesthesia, and his intravenous pyelogram shows no major abnormality. It was this patient and his subsequent course that led us to withhold radiation therapy in a neuroblastoma post-

operatively and, in a sense, we have built up a control series with surgery and no X-ray or chemotherapy, the mortality of which compares favourably with any series reported from our country in each of which X-ray therapy is given a major share of the credit for what survival there is.

In 1955 I reported a survival of 30.8% in the surgical management of neuroblastoma, that is 12 survivals of 44 patients. After presentation of this experience to several groups, the consensus was that if I had irradiated the patients as well I would have had an even better survival rate and, therefore, we planned a series of surgery followed by radiation. The next eight patients died following radiation and although eight is not a large number, it is a sufficiently large number for the surgeon to assess and perhaps change his tactics. When we reviewed the situation in 1958 we found that all the patients reported alive in 1955 were still alive in 1958 and one reported to be dead in 1955 (due to faulty follow-up) was indeed alive in 1958, and our survival was not 30.8% but 33.3% with a follow-up of 4 years 2 months minimum and 12 years maximum. Since reverting in early 1958 to the surgical extirpation of neuroblastomas without the benefit of radiation therapy, we again have several patients who seem on their way to the closest thing to a cure that one can talk about in the treatment of malignant disease in children.

The following are some examples of embryoma of the kidney.

Case 6. A 2½-year-old boy had an asymptomatic left upper quadrant mass found on routine physical examination by his paediatrician. An intravenous pyelogram showed a typical Wilms' tumour. The boy was immediately operated upon and treated with irradiation but metastases appeared in the liver and lung fields. The child died approximately one year after the appearance of metastases. In this instance the intravenous pyelogram revealed the usual garbled shadow produced by the dye in a Wilms' tumour (Fig. 6). In spite of the fact that this tumour was small, it metastasized early.

Case 7. R.K. This 7-month-old girl entered hospital because her mother had felt a huge abdominal mass while giving the child a bath. The mother, a competent observer, claimed that the tumour was not present the day before and the presumption is that haemorrhage into the tumour produced a change in size which led to its palpation. An intravenous urogram was done and this study revealed an intrinsic tumour in the left kidney (Fig. 7). The mass was removed and the child was given 2,500 R tissue dose to the midline. Seven years later she is alive and well with no evidence of metastases. Here, a huge tumour treated in the same way as in the previous patient showed no evidence of metastasis and has a seven-year cure.

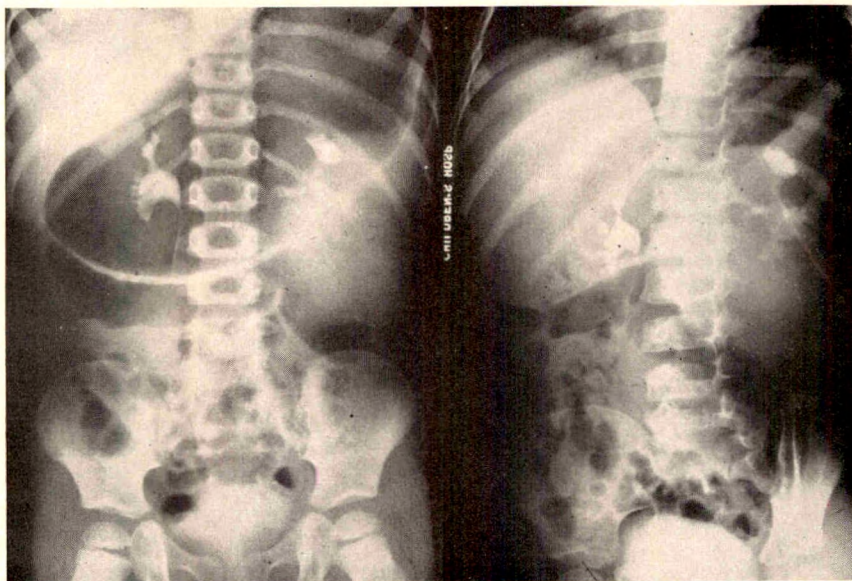


FIG. 6.—Case 6. Small Wilms' tumour with early metastasis.

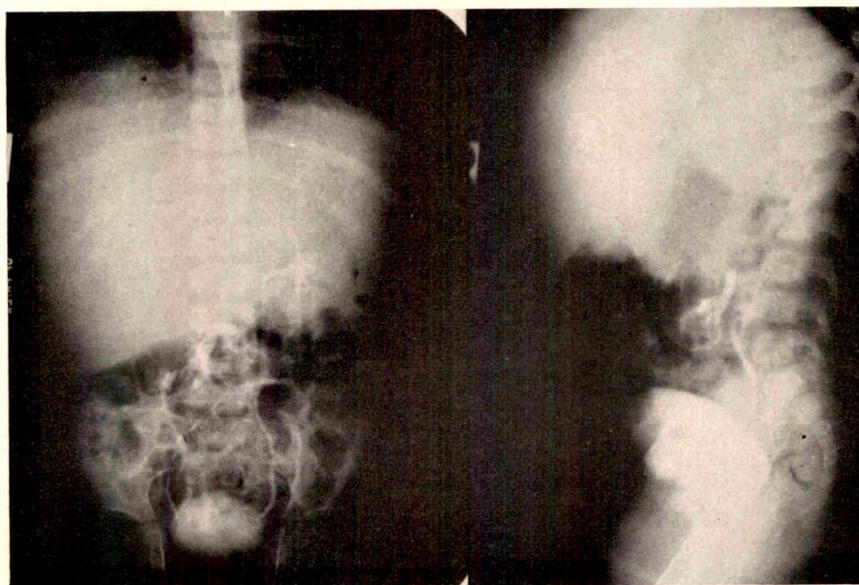


FIG. 7.—Case 7. Huge Wilms' tumour without metastases; seven-year survival.

Case 8. W.W. This 3-year-old boy went to see his family doctor for a routine prophylactic injection one week before admission. The physician, an unusually thorough gentleman, quickly palpated the abdomen as part of a routine check-up and felt the abdominal mass. Intravenous pyelography revealed a typical distorted and garbled opaque shadow indicating an intrinsic mass in the kidney (Fig. 8). The boy is alive and well eight years after surgery and X-ray therapy.

Case 9. E.Y. was a 1-year-old girl, who two weeks before admission was found by her father to have a mass on the right side. During the intervening two weeks her right side had become firm and rigid. Laxatives and enemas had been given in an attempt to remove what her father suspected was a faecal impaction. After surgery the patient developed metastases and died rather promptly. The anterior-posterior view in this child is not helpful. A lateral film was needed for a differential diagnosis between a neuroblastoma and a Wilms' tumour (Fig. 9).

Case 10. S.O. This 11-month-old girl was sent into hospital because someone thought he felt a mass in the left upper quadrant. At our institution no mass could be felt but intravenous pyelography was undertaken to rule out any doubt. This showed a very minimal distortion of the left renal pelvis. Our best films on this child are not available, but Fig. 10 indicates the area in which we were concerned. It was decided to do a nephrectomy rather than cut into the tumour, if such were present, for diagnosis, and when the kidney was removed it looked like a normal organ. When it was sectioned, however, there was a 2 cm. nodule just beneath



FIG. 8.—Case 8. Typically distorted pelvis by Wilms' tumour; eight-year survival.

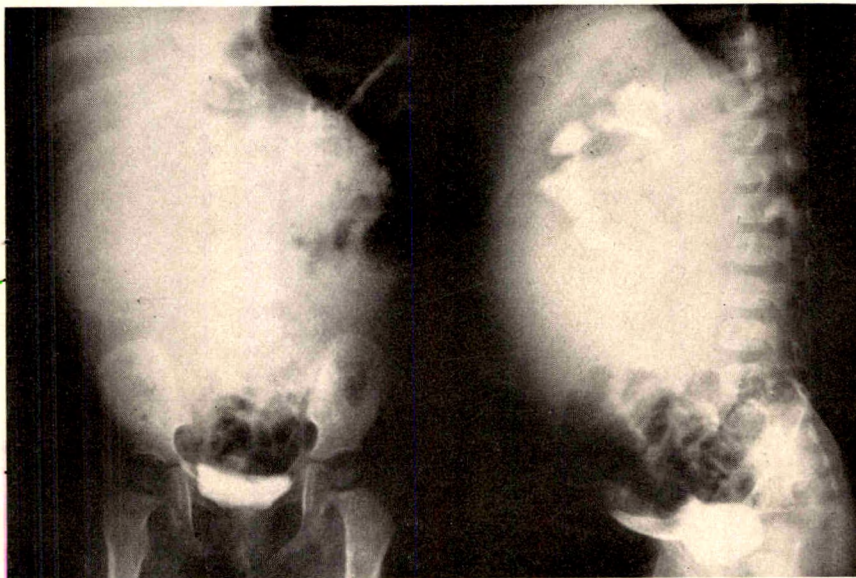


FIG. 9.—Case 9. Wilms' tumour. A-P view not helpful in making diagnosis; lateral film needed for differential diagnosis between Wilms' tumour and neuroblastoma.

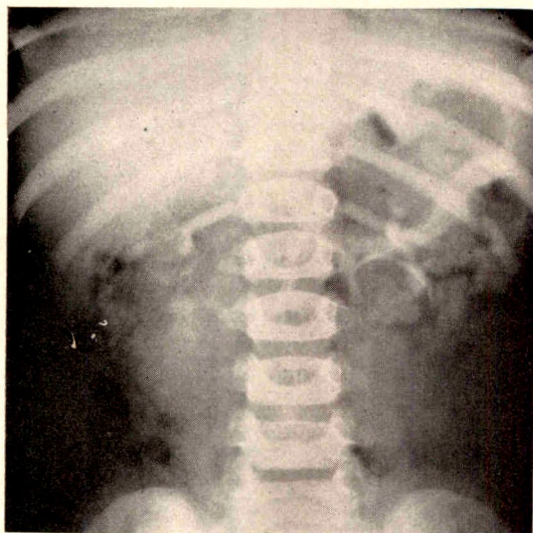


FIG. 10.—Case 10. Intravenous pyelogram showing crescentic displacement of calyx and pelvis on left due to a small Wilms' tumour. Compare with Fig. 11.

the renal pelvis. This proved to be a Wilms' tumour and the smallest one we have encountered clinically. The patient is alive and well four and a half years post-operatively. X-ray therapy was given.

Case 11. D.P. This 3-year-old girl with pyuria and fever was investigated for pyelonephritis by intravenous pyelography. In this study the same distortion of the left renal pelvis is noted as that seen in the previous patient's films. Note how the carbonated beverage has not only given better definition to the intravenous pyelography but has depressed the kidneys by intragastric gas pressure a distance of one vertebral body (Fig. 11).

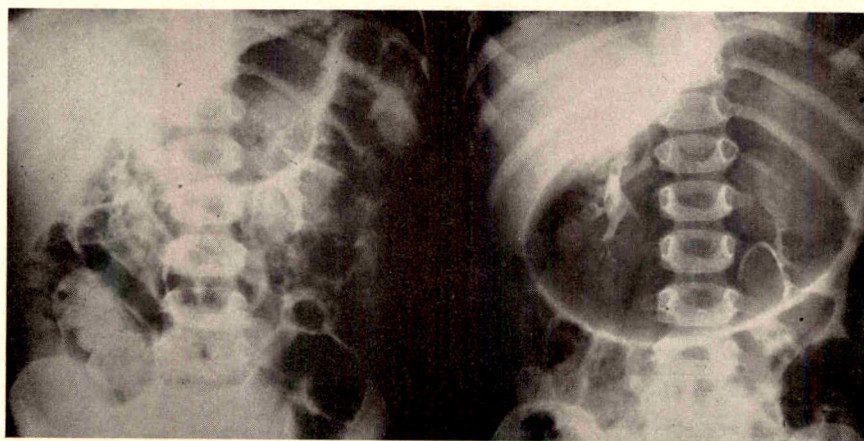


FIG. 11.—Case 11. Intravenous pyelogram showing crescentic displacement of calyx and pelvis on left due to an anomalous renal pyramid. Compare with Fig. 10.

Nephrectomy was carried out in this child and, to our great surprise, the distortion of the pelvis was by an anomalous pyramid. This is the first anomalous pyramid we have encountered and the second such X-ray picture in about 17,000 pyelograms. Obviously, this is not an adequate method of making a diagnosis of a small Wilms' tumour and on our next occasion we will resort to arteriography.

In summary, all the Wilms' tumours presented were asymptomatic. One such tumour was found on a routine physical examination by a paediatrician; another was found by a mother who claims it was not there the day before; a third was found when a local physician did a hurried physical examination before giving a prophylactic vaccine; a father discovered a fourth tumour and, finally, the fifth patient was thought to have a mass even when none could be palpated, but nevertheless proved to have the smallest clinical Wilms' tumour in our series.

Finally, to shake one's confidence in any diagnostic procedure, a normal kidney with an anomalous pyramid mimicked almost identically a Wilms' tumour.

None of these patients had haematuria, a sign which is usually interpreted as meaning a very poor prognosis because of early penetration of blood vessels. However, our own experience indicates that this might also be a very early sign and lead to a happy prognosis.

Although X-ray therapy is recommended as a routine post-operatively, patients are individually managed and when the tumour is small, the patient young, and the surgery atraumatic, no X-ray therapy is given.

Before leaving malignant tumours, we should again remind ourselves of the rapid growth of these two just discussed and the fact that the usual behaviour of adult cancer is crowded into a much shorter time in the paediatric age group. What is thought of as a five-year cure can usually be telescoped into a 14-month period in reference to the two tumours just discussed.

As to their importance, they account for 20% of all malignant tumours in children and 40% of those against which we have at the moment a satisfactory weapon.

The following are some other abdominal tumours which occasionally present themselves for differential diagnosis.

Case 12. F.L. A 2½-year-old girl entered hospital because of an anaemia. The evacuation of some of the barium enema revealed an abnormal air-filled bowel in the right upper quadrant which, when we did the small bowel study, filled with barium. The patient was sent home but returned bleeding severely from the rectum and was operated upon. Her lesion proved to be an ulcerated duplication of the ileum (Fig. 12).

Case 13. R.S. was a 5½-month-old girl who at the age of 3 weeks was found to have a large liver. Nothing was done for this child until she came to our hospital at 5½ months when she was really a huge abdomen with a small baby attached. She was completely dehydrated from vomiting and could not hold anything in her stomach. A survey film revealed a huge abdominal mass on the right side thought to be liver. With some barium in the stomach the edge of the mass could be seen.

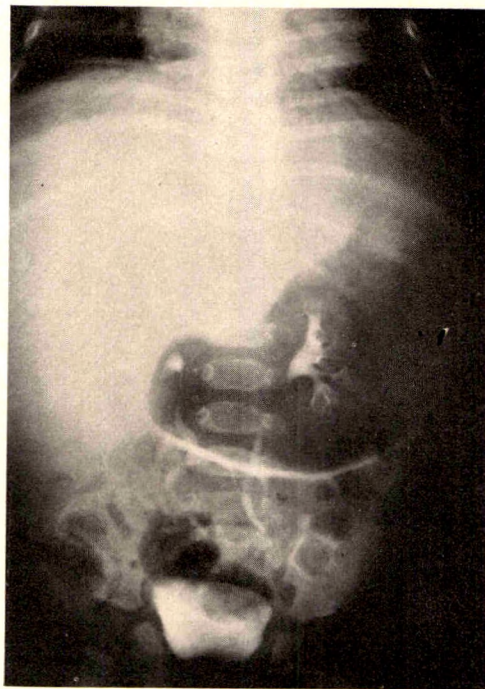


FIG. 13.—Case 13. Tumour of liver, affecting chiefly right lobe. Haemangioendothelioma.

An intravenous urogram proved that this was not intrinsic to the kidney (Fig. 13). At operation it was

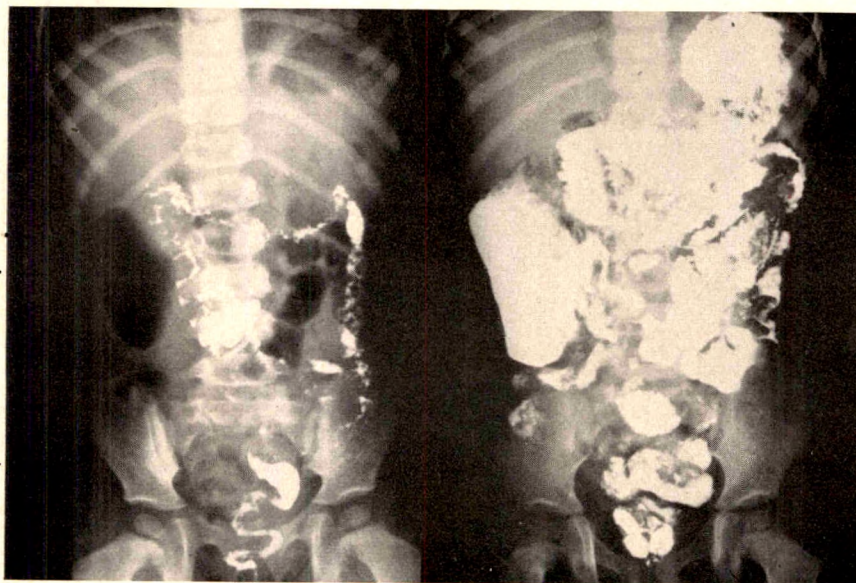
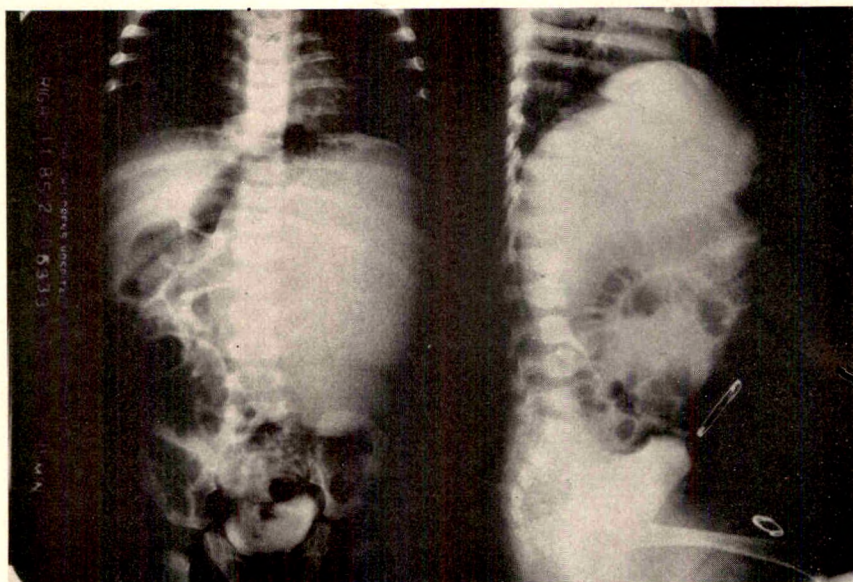


FIG. 12.—Case 12. Duplication of ileum. Film on left shows lesion outlined with gas, on right filled with barium.

FIG. 14.—Case 14. Huge hepatoblastoma of left lobe before radiation therapy.



thought that we were dealing with a primary carcinoma of the liver but a piece taken for biopsy was reported as being a benign haemangio-endothelioma. The child received 1,000 R tissue dose to the liver which had shrunk to normal size in eight months. The child is alive and well several years later.

Case 14. J.M. was a 2½-year-old boy with progressive enlargement of his abdomen of one month's duration. The flat film showed a huge mass and the intravenous pyelogram showed the kidney to be depressed so that a diagnosis of neuroblastoma was made (Fig. 14). At operation the tumour was found to be intrinsic to the liver and the mass seemed to involve both right and left lobes. The child was given 3,200 R tissue dose in 33 days through a portal 13×15 cm. Eight weeks after X-ray treatment the child was re-explored and the tumour was found to lie in the right lobe only. A right hepatic lobectomy was carried out and the child is alive and well

five years post-operatively. The histological diagnosis was hepatoblastoma.

Case 15. N.L. This 4½-year-old girl had a six-week history of lower abdominal pain which eventually became epigastric. Three weeks before admission she became jaundiced and had clay-coloured stools. The gastro-intestinal series of radiographs undertaken at another hospital showed a wide duodenal loop which would have suggested in an adult carcinoma of the head of the pancreas (Fig. 15). The child was operated upon in our institution five days after the study elsewhere and she did indeed have a tumour in the region of the head of the pancreas which proved on histological section to be a reticulum cell sarcoma. The tumour involved the coeliac axis and was not resectable. The child received 2,800 R tissue dose over a portal of 15×15 cm. over a period of three weeks. She did well for a while but six months after operation she came into hospital in coma

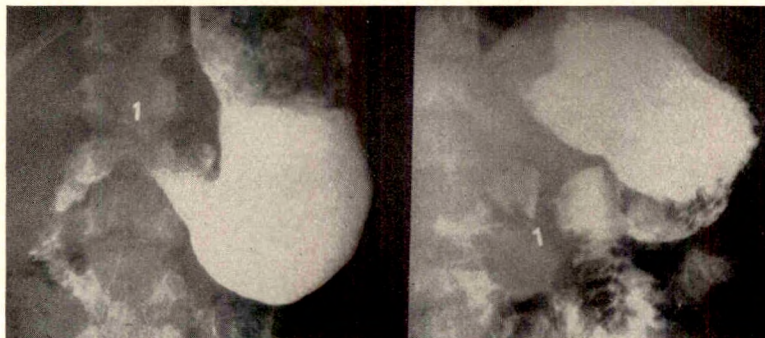


FIG. 15.—Case 15. Widening of duodenal loop caused by reticulum cell sarcoma simulating classical carcinoma of head of pancreas.

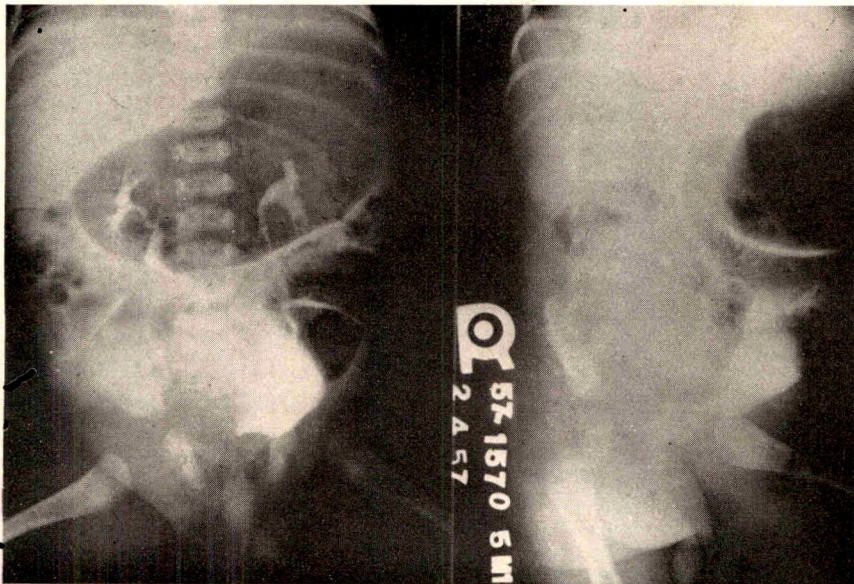


FIG. 16.—Case 16. A-P and lateral intravenous pyelogram for abdominal mass which proved to be iliac abscess secondary to an infected circumcision.

and died. At autopsy she was found to have radiation nephritis as the cause of her death.

Case 16. This 2-week-old boy had a swollen leg and prominent veins over the right lower quadrant. It was thought that this would be a neuroblastoma on the basis of clinical impression. It proved, however, to be a staphylococcal abscess secondary to a dirty circumcision and inguinal adenitis (Fig. 16).

Case 17. J.A. Eleven days before this examination this 6-year-old boy was struck in the epigastrium by the handlebars of a bicycle. From that time on he had upper abdominal pain and vomiting. His serum amylase was 1,500 units. Original films show the appearance of a mass in the vicinity of the pancreas which had not altered when repeated two weeks later (Fig. 17). The child was treated by judicious neglect and had no further difficulty.

Case 18. E.T. This 11-year-old boy complained of jaundice of one month's duration and loss of appetite. He entered the Children's Hospital of Philadelphia with a temperature of 105° F. and abdominal pain; gastro-intestinal series of radiographs showed his common bile duct to be large as indicated by the depression of the duodenum (Fig. 18). The child was operated upon and a huge gall bladder and dilated common duct were found. The duct was opened and there extruded a number of flimsy structures resembling nasal polyps. A T-tube was left in the common bile duct and a cholangiogram indicated dilatation of the entire intrahepatic biliary tree. The patient died two months after operation and at autopsy had a large abdominal tumour as well as metastases in the abdomen, pelvic bones and liver. This, of course, is the classical early and late picture of a rhabdomyosarcoma.

Case 19. C.B. was a 4-year-old female who was admitted to hospital because of abdominal pain of one

week's duration. An abdominal mass could be palpated in the left upper quadrant separate from the left kidney. At operation this proved to be a teratoma which was almost a complete embryo with arm and leg buds. It was necessary to remove the left kidney and left adrenal gland in the course of the dissection (Fig. 19).



FIG. 17.—Case 17. Displacement of bowel caused by pseudocyst of pancreas 11 days after epigastric injury.

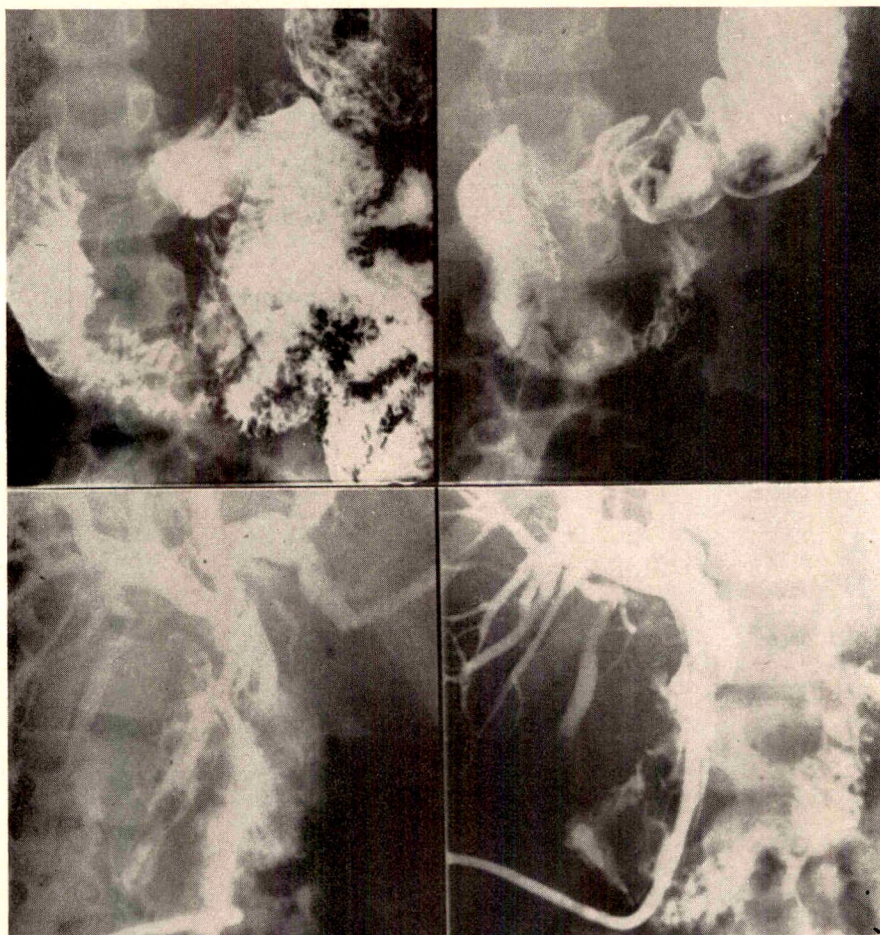


FIG. 18.—Case 18. Upper gastro-intestinal series showing interruption of barium shadow in duodenum due to an enlarged common bile duct. Cholangiogram shows dilatation of common bile duct and its proximal intra-hepatic radicals.

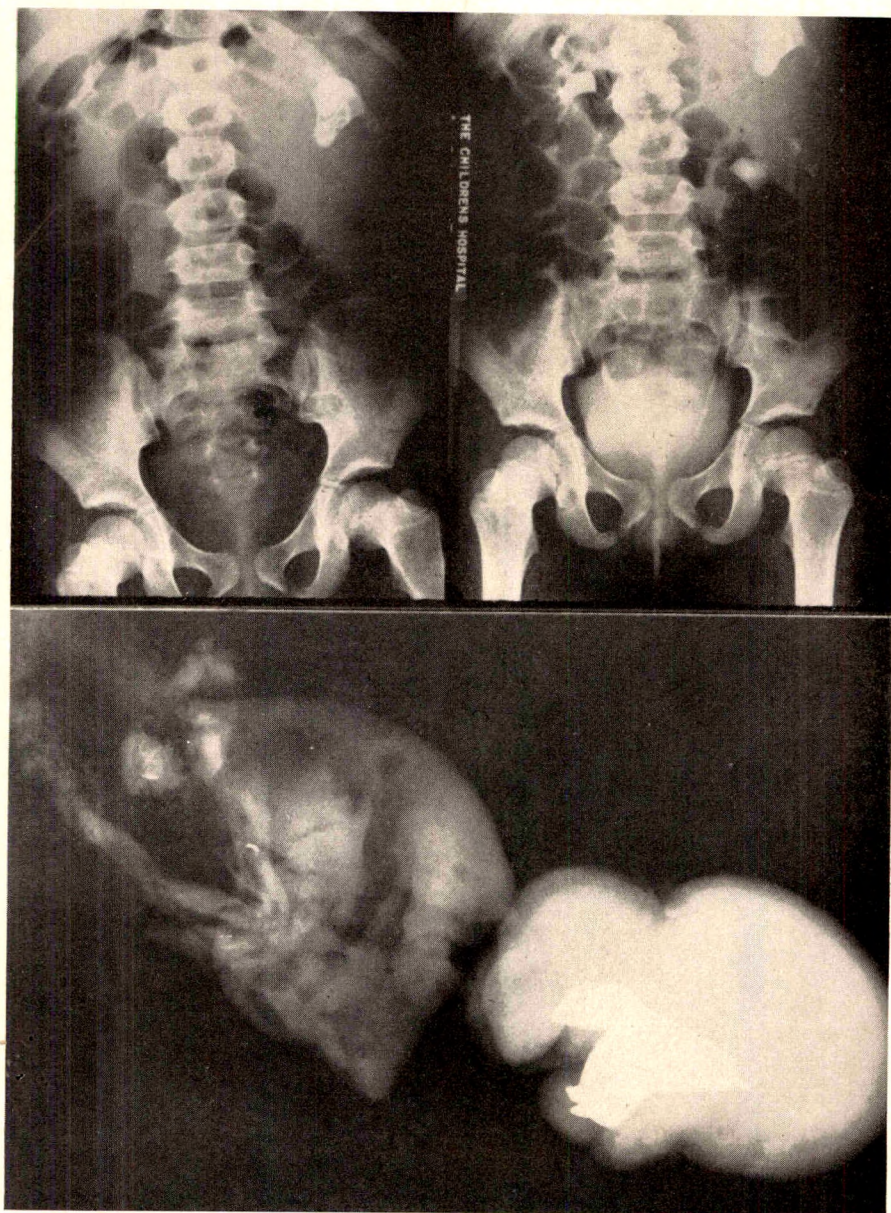


FIG. 19.—Case 19. Intra-abdominal teratoma attached to left kidney and adrenal gland, with X-ray of teratoma following extirpation.

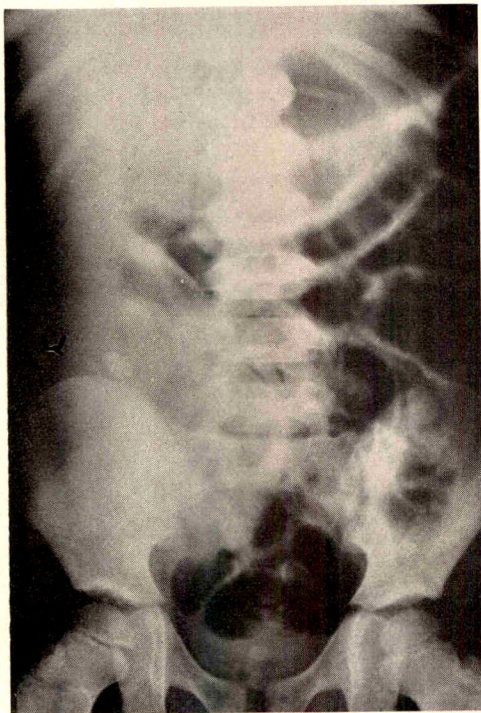


FIG. 20.—Case 20. Abdominal mass containing faecolith of calcific density; appendiceal abscess.

Case 20. D.P. was a 5½-year-old male with a two-week history of abdominal pain. In this two weeks the pain had become worse and the child had begun to vomit. At the time of examination there was severe abdominal tenderness and a mass could be palpated in the right lower quadrant. The films revealed a large soft tissue mass and a calcified mass within the large soft tissue density. This proved to be an appendiceal abscess with a faecolith (Fig. 20).

Case 21. T.E. A 6-month-old girl entered the hospital with a referring diagnosis of Wilms' tumour. On palpation of the abdomen there was a huge mass and, since palpation in the left upper quadrant moved the mass in the right upper quadrant and vice versa, the presumptive diagnosis was a Wilms' tumour in a horseshoe kidney. A flat plate of the abdomen revealed what looked like an old barium enema of the colon. Since there was no such history, it was presumed that the shadow represented calcifying faeces. A barium enema was carried out as a terminal aganglionic segment indicating megacolon was suspected. It was impossible to wash out the faecal impaction and at operation a colostomy was done. Six months later at the time of attempted pull-through procedure two lumina were noted in the bowel. It was then understood that we were dealing with a duplication of the colon. In the original films it was possible to see an air column streaking past the impaction of calcific density. The bowel was re-anastomosed after resecting the common wall between the two duplications (Figs. 21, 22, 23).

Case 22. L.S. This 3-year-old girl came into hospital because of pain in her left hip of one year's

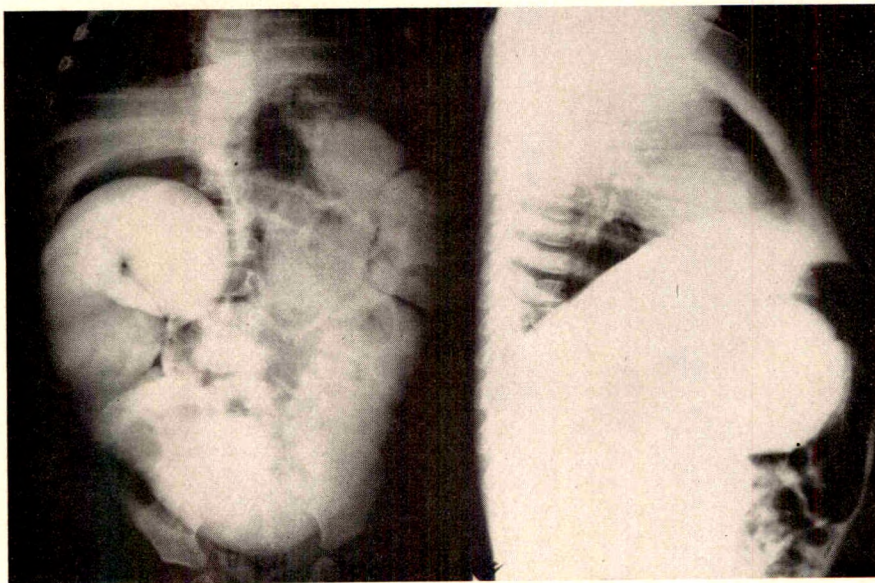


FIG. 21.—Case 21. Faeces of calcific density in duplication of colon with blind distal end.

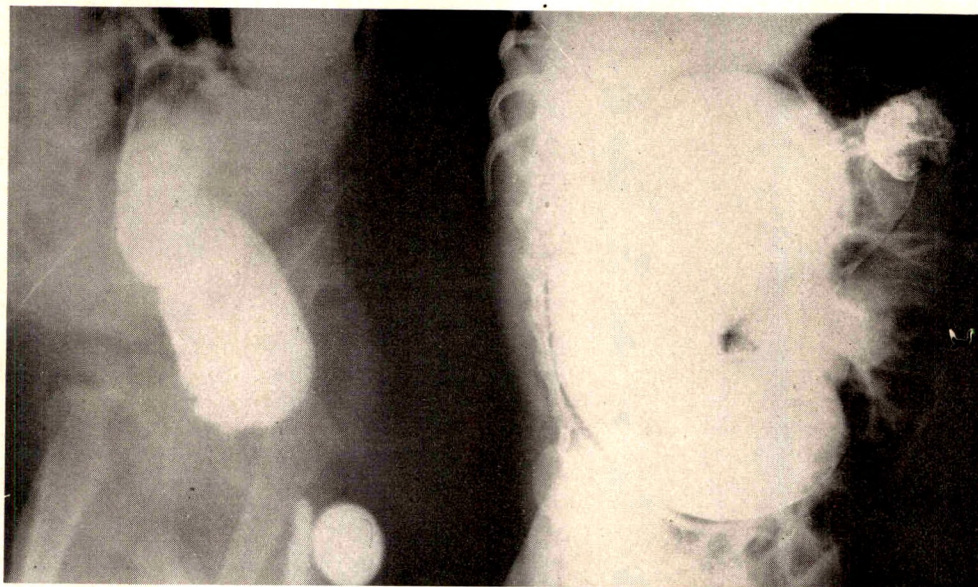


FIG. 22.—Case 21. Barium enema of patient in Fig. 21. Note air column to left in lateral film indicative of true colon.



FIG. 23.—Case 21. Post-operative barium enema showing duplication proximally and single lumen distally.

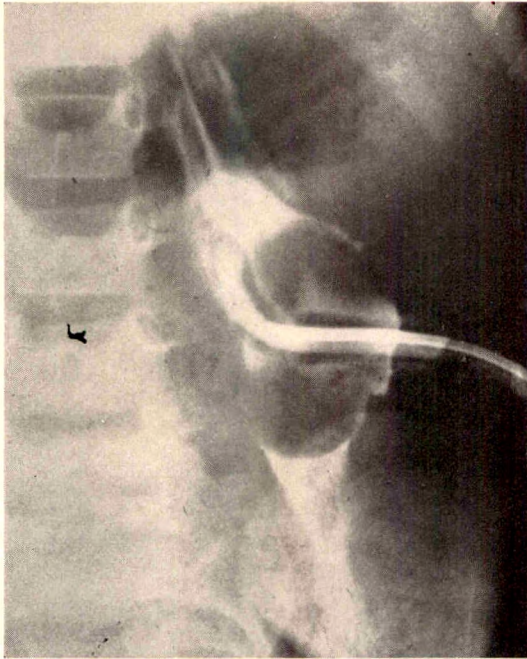


FIG. 24.—Case 22. Post-operative film showing catheter in retroperitoneal cavity communicating with duplication of stomach (neurenteric cyst?).

duration. She had been studied in several hospitals for this period of time. The films of her pelvis were normal but a mass lesion was found in the left mid-abdomen which seemed to be extrinsic to the left kidney. At operation there was a retroperitoneal mass lying beneath the mesentery of the colon. On aspiration this produced thick material resembling motor oil which was evacuated. It was then obvious that an hour-glass constriction connected this sausage-shaped mass with a much larger mass which lay within the psoas muscle. This latter mass also contained the same thick grumous material.

Further dissection revealed that the initial mass was a cystic structure with a lining somewhat resembling that of the stomach. It perforated posteriorly into a pseudocyst of the psoas muscle. Microscopical sections revealed gastric mucosa. This was a duplication of the stomach without attachment to any other intestinal viscus (Fig. 24). In all likelihood with further dissection this lesion could have been proved to be a neurenteric cyst.

One could continue to discuss abdominal tumours for a considerable period of time, calling upon experience with the commonplace as well as the bizarre. I trust these few examples of abdominal masses have served to place in proper focus the more serious and challenging aspect of the management of abdominal tumours in children, namely those malignant lesions which carry such a forbidding mortality.

OVARIAN NEOPLASMS IN CHILDREN*

BY

ISABELLA FORSHALL

From the Royal Liverpool Children's Hospital and Alder Hey Children's Hospital, Liverpool

Just over 100,000 cases have been admitted to the two main Liverpool Children's Hospitals during the last 10 years; amongst these were 21 children with ovarian new growths (Table 1).

TABLE 1
OVARIAN NEW GROWTHS, 1949-59

Tumour	No. of Cases	Left	Right
Cystadenoma	2	1	1
Teratoma:			
(a) Benign cystic	12	7	5
(b) Solid	1	—	1
Tumours of special morphology	3	3	—
Tumours of doubtful origin (one case had bilateral tumours)	3	3	1
Total	21	14	8

Cystadenoma

Cystadenoma, which accounts for 40-50% of all ovarian new growths, is a tumour of adult life, and uncommon in patients under 20 years of age. We have seen two cases, a girl (E.G.) of 13 with a right-sided, thin-walled, unilocular cystadenoma measuring $17 \times 13 \times 10$ cm., and a 12-year-old child (M.O.) with a small, left-sided, multilocular cystadenoma; neither of these two girls had menstruated.

Teratoma

Including all age groups, teratomas constitute 10-15% of ovarian tumours, but over 50% of the tumours of children are of this type. Willis (1955a) succinctly defines teratomas as 'embryonic tumours of pluri-potential, regionally non-specific tissue'. They possibly originate in foci of plastic polyvalent tissue, which escape the influence of the primary organizer (Willis, 1955b). Ovarian teratomas are arbitrarily divided into:

- (a) the common, benign, largely cystic tumours, in which tissue differentiates and matures

synchronously with the tissues of the host; and

- (b) the much less common solid or polycystic tumours, in which a great variety of tissue in different stages of maturity is found. They may grow rapidly and are usually malignant.

Though benign cystic teratomas consist largely of ectodermal tissue, skin with sweat glands and hair follicles, tooth buds or teeth and sebaceous material, endodermal and mesodermal tissue is always represented. Cartilage, muscle, intestinal and bronchial epithelium and nervous tissue are common. The contents of the cyst may be mucous or cerebrospinal fluid, in addition to or to the exclusion of the more usual sebaceous material.

The right ovary is affected more often than the left, and in 10% of cases there are bilateral tumours.

Radiological examination shows teeth, cartilage, bone or calcification in the cyst wall in 75% of cases.

Ovarian teratomas have been described in infants. They are, however, rarely encountered in children under 3 years of age. In a child the cyst is seldom larger than the patient's head.

Children with teratomatous cysts present in three ways: with enlargement of the abdomen; with abdominal pain, which may be either continuous or intermittent; or as urgent emergencies with torsion of the cyst pedicle.

Torsion is the commonest complication and is recorded in 1 in 4 or 1 in 3 of large series of cases (Peterson, Prevost, Edmunds, Hundley and Morris, 1955).

The development of carcinoma in a benign cystic teratoma is not uncommon in adults, usually in those past middle life, in whom the tumour has probably been present for a long time. It is doubtful whether this complication ever occurs before puberty.

We have seen 12 children with teratomatous cysts; the main features of these cases are summarized in Table 2.

Solid or polycystic teratomas are, by and large, rapidly growing and highly malignant. They tend to metastasize via the blood stream to the lungs.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

TABLE 2
BENIGN CYSTIC TERATOMAS

Case	Age (yr.)	History	Radiograph	Torsion	Side	Histology
S.J.	3	4 wk. pain, vomiting, constipation	Positive	Yes	Left	Teratomatous cyst; sebaceous material, hair, teeth, muscle
E.L.	10	3 yr. pain left-sided	Positive	No	Right	Teratomatous cyst; sebaceous material, hair, teeth
R.S.	5	Increasing abd. swelling; pain	—	No	Right	'Dermoid cyst', very large
H.C.	8	Increasing abd. swelling	—	Yes	Left	'Dermoid cyst'
C.P.	10	3 mth. intermittent left abd. pain; vomiting; pain on defaecation	—	Yes	Right	'Dermoid cyst', twisted with one horn of bicornate uterus
J.R.	7	Abd. pain and vomiting	Negative	Yes	Left	'Dermoid cyst'
C.W.	10	Abd. enlargement, pain	Positive	No	Left	Teratomatous cyst; skin, hair, cartilage, brain
B.G.	11	2 yr. abd. pain; nausea	Negative	No	Left	'Dermoid cyst'
W.T.	12	2 yr. vague pain; 3 wk. severe pain	Positive	No	Left	Teratomatous cyst; skin, teeth, hair, bone, cartilage, lung, nervous tissue
R.C.	5	Enlargement of abdomen since birth	Positive	No	Right	Teratomatous cyst; 12 × 1 × 6 in.
P.M.	11	Few mth. intermittent abd. pain	Positive	No	Left	Teratomatous cyst; calcified wall, bone muscle, tooth, columnar epithelium 13 × 10 × 8 in.
L.S.	13	Few days left-sided abd. pain	Positive	No	Right	Teratomatous cyst; hair, sebaceous material, cartilage, mucous glands, columnar ciliated epithelium; cyst lined squamous epithelium 10 × 6 × 4½ in.

Very rarely precocity and uterine bleeding have been associated with malignant teratoma containing areas of chorionic carcinoma.

We have seen only one solid teratoma; it occurred in a 12-year-old girl (J.N.) who had a large, easily visible, abdominal swelling. At operation there was bloody peritoneal fluid and the tumour had transgressed its capsule at two points; it was considered to be malignant. The pathologist, however, reported that, though the tumour contained the typical conglomeration of tissue, there was no definite evidence of malignancy. The child is well four years post-operatively.

Tumours of Special Morphology

(a) **Granulosa Cell Tumour or Granulosa Cell Carcinoma, and Theca Cell Tumour.** These tumours contain cells similar to those of the zona granulosa and theca interna of the normal ovary. Willis (1948) believes that they originate in normal follicular tissue or from the bi-potential formative ovarian stroma. Granulosa cell tumours usually contain some theca cells and, though theca cell tumours are more often 'pure', they often contain areas in which granulosa cells can be found. The rare luteal tumour causing similar symptoms is probably a granulosa-theca cell tumour which has undergone luteinization.

In keeping with tumours of other endocrine glands, granulosa and theca cell tumours may, or may not, produce hormones.

Granulosa cell tumours are said to constitute 10% of all solid ovarian tumours; 5% of the total number recorded have occurred in children (Morris and Scully, 1958a). This estimate of the relative fre-

quency of the tumour in children is probably too high. A hormone-secreting tumour in a child would almost certainly be published, whilst such a tumour in an adult might well cause less interest. Wilkins (1957) states that 33 granulosa cell tumours causing precocious puberty in children of 7½ years or under have been recorded. He has followed the exacting discipline of paediatric endocrinology for 20 years and has seen only a single case. Morris and Scully (1958b) state that 60 granulosa cell tumours and four theca cell tumours have caused precocious sex changes in prepubertal children. The disparity between 33 and 60 probably reflects a difference of opinion between the two authorities about the age at which sex changes are considered to be precocious. The youngest reported case of a granulosa cell tumour is a 14-week-old infant with bilateral tumours (Zemke and Herrell, 1941).

Uncommon as the granulosa cell tumour is, it is the most frequent ovarian cause of sexual precocity. The oestrogen-secreting tumour causes enlargement of the uterus, endometrial hyperplasia and bleeding, which may be slight or profuse, continuous or intermittent. In about half the reported cases it has been cyclical. Bleeding may occur only after removal of the tumour (oestrogen-withdrawal bleeding); on the other hand, it has often been the initial symptom; it is anovular and the other ovary remains normal for the child's age. There is development of the vulva and vagina and the vaginal cytology is of adult type.

Secondarily induced development of the breasts and growth of sexual hair commonly occur but are not invariable. Body growth is stimulated and the child is likely to be tall for her age.

Unfortunately few oestrogen assays have been made in children; in those recorded, the urinary oestrogen figures have varied from normal adult to very high levels (Wilkins, 1957).

As first pointed out by Gross (1953), all granulosa cell tumours, which have caused symptoms of oestrogism in children, have been readily palpable on abdominal examination. This is an important point in the differential diagnosis of bleeding or of sexual precocity.

In adults, symptoms of hyperoestrinism have been produced by tumours as small as 1.5 cm. in diameter. It is therefore possible that cell for cell the granulosa cell tumours of children produce less oestrogen than the tumours of adults.

In children under 8 or 9 years, the age at which the ovary normally begins to undergo pre-pubertal changes, regression of sexual development takes place after removal of a granulosa cell tumour. In children over this age little change occurs apart from cessation of bleeding and reduction in the size of the uterus.

No long-term follow-up of cases which have had granulosa cell tumours removed in childhood is available. It is, however, known that a second tumour may develop in the other ovary many years after a granulosa cell tumour has been removed, and that intraperitoneal recurrences may appear a long time after a patient is thought to be cured (Diddle, 1952). Distant metastases may occur but are not common. The mortality for granulosa cell tumour in adults is about 50% and the longer the follow-up the higher the mortality. The histology of the tumour may give some help in prognosis (Kottmeier,

granulosa cell tumour (Table 3). She was admitted aged 11 months with a cystic, easily palpable tumour which had undergone torsion. Enlargement of the breasts was just appreciable, and there was a faint down of dark pubic hair. There was no history of bleeding, but she had a slight blood-stained vaginal discharge for 48 hours after operation.

(b) **Arrhenoblastoma, Hilar Cell or Sertoli-Leydig Cell Tumour.** These tumours, which characteristically cause masculinization, are rare at any age, and excessively rare before puberty. An arrhenoblastoma in a girl of 11 years with symptoms of masculinization is, however, described (Thomas, Fisher, Turnbull and Krieger, 1952) and Morris and Scully (1958c) mention a Leydig cell tumour causing virilism in a girl of 4 years.

(c) **Germinoma.** This is a non-hormone-secreting tumour, composed of cells of embryonal type, resembling the sexually undifferentiated germ cells of the early gonad.

Disgerminoma of the ovary is histologically indistinguishable from seminoma of the testicle. The former has a high incidence in pseudo-hermaphrodites and patients with hypogonadism, and seminoma has a predilection for incompletely descended testes; either tumour is occasionally bilateral. Interesting differences are that, in spite of seminoma being more easily diagnosed whilst the tumour is small, the mortality for seminoma is higher than that for disgerminoma. The difference in age incidence is very remarkable. Disgerminoma is a tumour of the young; three-quarters of the cases recorded have been under 30 years and half under 20 years, though no instance of the tumour has been

We have seen only one child (C.E.) with a

TABLE 3
TUMOURS OF SPECIAL MORPHOLOGY

Case	Age	History	Clinical Findings	Treatment	Diagnosis	Side	Result
C.E.	11 mth.	Abdomen always prominent; rapid increase last few days; acute abdominal pain; vomiting	Large cystic lower abd. tumour; definite slight mammary enlargement; faint down of dark pubic hair	Oophorectomy	Granulosa cell tumour; large polycystic; uterus enlarged, other ovary normal; torsion	Left	Post-operative uterine bleeding; complete regression of sex changes; well 3 yr.
J.B.	12 yr.	Abdominal pain; dysuria; pyrexia	'As big as a child of 8 yr.'; large solid tender mass left lower abdomen and pelvis	Excision of tumour, uterus, ovary, part of bladder, sigmoid colon and parietal peritoneum; radiotherapy	Disgerminoma; solid tumour as big as large grapefruit; adherent to and infiltrating pelvic organs and parietal peritoneum	Left	Still very small; well 2½ yr.
J.D.	13½ yr.	(At 3 yr. undescended testes, right gonad biopsy, testes, repair hypospadias); acute abdominal pain 6 days	Large lower abd. tumour; urinary 17-ketosteroids 4 mg./day; sex chromatin —negative, male	'Oophorectomy'; radiotherapy	Germinoma; ?disgerminoma; ?seminoma; large solid tumour, small uterus, fallopian tubes and broad ligaments; torsion	Left	Well 6 mth; growth of penis and sexual hair

recorded in a child under the age of 7 years. Seminoma is most frequent early in the fifth decade, very rare before 20 years, and the youngest case recorded was 16 (Bell, 1938).

Disgerminoma is a smooth, solid tumour, grey or greyish-pink in section. It has a tendency to undergo necrosis, to transgress its capsule and invade neighbouring pelvic organs and sometimes lymphatic glands. Distant metastases occur, but uncommonly. In cases followed up over long periods the mortality is about 50% (Morris and Scully, 1958d).

Our first case (J.B., Table 3) apart from her tumour showed no abnormality except that she was very small for her age. She is chromatin-positive.

The second case (J.D., Table 3) occurred in a child who is chromatin-negative. The gonad on the left was entirely replaced by tumour, so that it is not possible to know whether it was an ovary, a testis or an ovo-testis. The tumour was intra-abdominal and there was a uterus and two fallopian tubes; the other gonad is, however, an incompletely descended testis. The child's development since the tumour was removed appears to be conforming to the male pattern. In view of the patient's age, this tumour is best designated a germinoma rather than either a seminoma or disgerminoma.

Tumours of this group which, from their morphology, would be expected to secrete oestrogens or androgens may be inactive; less commonly, a tumour containing granulosa cells produces androgens and a tumour containing Sertoli-Leydig cells causes feminization.

Germinomas, which are characteristically non-hormone-secreting, have occasionally produced sex hormones.

Tumours of Doubtful Origin

Three cases have been grouped under this heading (Table 4).

One was a highly malignant anaplastic carcinoma in a girl (J.T.) of 13 months, which conformed histologically to the tumour described by Schiller (1939) as a mesonephroma. Morris and Scully (1958e) include this growth amongst the malignant teratoid tumours.

The second was a large, solid tumour in a girl (J.C.) of 8½ years. Histologically it was a highly malignant undifferentiated carcinoma. The possibility of its being a hormonally inactive granulosa cell carcinoma, or even a disgerminoma, is not excluded: in favour of one or other of these diagnoses is the fact that the child is well four and a half years after operation and radiotherapy.

The third child (V.T.) presented during life, and at autopsy, a picture so confusing that the case is left without comment.

Secondary malignant tumours of the ovary are common in adults, but in children they are very rare; Grob (1957) has described bilateral ovarian tumours secondary to lymphosarcoma of the neck. In this case a very careful search at autopsy disclosed no alternative primary growth.

Treatment

An ovarian tumour should be removed, and the sooner the better; it may be malignant and a few days may make a difference in prognosis. A large incision should be made, and the pedicle of the tumour should be clamped at the first possible

TABLE 4
TUMOURS OF DOUBTFUL ORIGIN

Case	Age	History	Clinical Findings	Treatment	Diagnosis	Side	Result
J.T.	13 mth.	Enlargement of abdomen	Firm, mobile abdominal tumour	Oophorectomy	Anaplastic carcinoma (mesonephroma)	Left	Death 4 mth. Abdominal metastasis
J.C.	8½ yr.	Enlargement of abdomen	Large, solid, lower abdominal tumour	Oophorectomy ; radiotherapy	Solid; tumour through capsule; blood and clumps of tumour cells in peritoneal fluid; undifferentiated carcinoma; ?? granulosa cells. W. 435 g.	Left	Well 4½ yr.
V.T.	13 yr.	2 mth. general ill health, pain, anaemia, intestinal bleeding	Abdominal and pelvic mass; ascites; clinical features and blood picture of widespread malignant process	Radiotherapy started but discontinued	Autopsy: bilateral ovarian tumours; search revealed no alternative primary growth. Histological features of anaplastic carcinoma rather than malignant reticulo-endothelial disorder; probably primary ovarian growth	Left.	Death

moment to prevent dissemination of malignant cells via the blood stream.

The fallopian tube should be preserved in obviously simple cystic tumours. The second ovary should be examined; it may contain a small teratoma or granulosa cell tumour, removal of which by dissection will preserve some ovarian tissue.

Cases of granulosa cell tumour and dysgerminoma have recovered when the tumour has spread beyond its capsule and invaded other pelvic organs so that radical excision is justified and may be rewarding.

There is little authoritative guidance about when to use, and when not to use, radiotherapy, and the decision may be very difficult. Not only will irradiation cause sterility, but growth and the pattern of growth may be impaired.

It is probably true to say that anaplastic carcinomas, malignant teratomas and tumours which histologically resemble chorionic carcinoma will be little influenced by radiotherapy.

Granulosa cell tumours and dysgerminomas are radio-sensitive, and there is definite evidence that in adults the prognosis, after removal of these tumours, is improved by radiotherapy (Santesson, 1947). Therefore, if it has been necessary to remove as well as the tumour the uterus and second ovary, or if the peritoneal fluid contains tumour cells, or if the report of the pathologist suggests a highly malignant growth, radiotherapy should be given.

If the tumour is intracapsular and the pathological report is favourable, x rays should be withheld.

Girls who have had both ovaries removed, or one removed and the other destroyed by x rays, should have the benefit of endocrine treatment at 13 to 16 years of age so that they may, as far as possible, conform to the female pattern.

The literature shows that ovarian tumours are more frequently right- than left-sided, and this is especially true of teratoma and dysgerminoma.

In this series of 21 cases (22 tumours), 14 were left-sided and eight right-sided (Table 1). This emphasizes the fallacies inherent in conclusions based on small series of cases.

I gratefully acknowledge the help of Dr. E. G. Hall and Dr. J. S. Elwood, pathologists to the two hospitals, and thank Mr. P. P. Rickham for allowing me to include some of his cases.

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PRIMARY TUMOURS OF THE LIVER IN INFANTS AND CHILDREN*

BY

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Primary liver tumours occur in infants and children with sufficient frequency to justify careful evaluation of current techniques in diagnosis and management and to review the pathological classification of this group of neoplasms. In the past nine years (1950-1958) 15 such cases have been diagnosed at the Columbus Children's Hospital, all presenting as clinical problems; an analysis of these cases forms the substance of this report. During the same period of time 46 cases of neuroblastoma and 17 cases of embryoma of the kidney (Wilms' tumour) have been treated at this institution.

Although the treatment of liver tumours, as judged from a résumé of individual case reports in recent years, has been encouraging, the overall results achieved in significant series have been disappointing and have perhaps fostered a generally hopeless outlook for young patients with such lesions (Donovan and Santulli, 1946; Wangensteen, 1951; Lortat-Jacob and Robert, 1952; Quattlebaum, 1953; Brunschwig, 1953; Pack and Baker, 1953; Lorimer, 1955; Clatworthy and Boles, 1956). In the series from Babies' Hospital in New York City analysed by Andersen (1951) there was only one long-term survivor in 12 cases occurring over a 15-year period. This patient remained well over a six-year follow-up period after excision of the left lobe of the liver had been performed for a mesenchymoma. Gross, in a review at the Boston Children's Hospital, reports two apparent cures out of 18 such cases. One of these received radiotherapy for multiple haemangiomas and has been in excellent health for seven years thereafter; the second has been well over a 10-year period after having a wedge resection of a small haemartoma.

Safe techniques for the resection of the left lobe of the liver have been available for many years, and

there are numerous reported successful cases of this procedure applied to removal of neoplasms confined to this lobe. Most of these were performed on adult patients, but a number were in children. More recently the technique for total resection of the right lobe of the liver was evolved, whereby the dangers of haemorrhage, air embolism, bile peritonitis and subsequent liver failure are minimized (Wangensteen, 1951; Lortat-Jacob and Robert, 1952; Brunschwig, 1953; Pack and Baker, 1953; Quattlebaum, 1953; Lorimer, 1955). The application of one or the other of these procedures should permit the surgical excision of most liver tumours which are not centrally placed or diffuse or multicentric lesions.

Diagnosis

The vast majority of primary neoplasms of the liver produce symptoms in the first two years of life. Only two of the 15 cases in this series had the onset of symptoms after 2 years of age, and in three instances the clinical manifestations were present in the neonatal period.

Abdominal enlargement due to a palpable abdominal mass is by far the most common presenting complaint. The distribution of these tumours in the liver, and hence the location of the mass, seems to follow the distribution of the liver mass. Of these 15 tumours, nine were in the right lobe, three in the left and two were situated centrally. One was diffuse. In most instances the mass was in the right upper quadrant, and less often in the mid-epigastrium. The mass moves with respirations. Its characteristics on palpation vary considerably, but most tumours are hard and rounded and inseparable from the liver edge. Transillumination is a useful tool in diagnosis since a liver tumour which transilluminates is almost certainly a large lymphangioma.

Other clinical manifestations observed in this

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

series include anorexia, fever, weight loss and rarely jaundice. This latter sign was observed in only a single case in this series, a 14-year-old girl who died from a liver cell carcinoma associated with post-necrotic cirrhosis. In a single instance, heart failure in a newborn infant progressed to death at 8 weeks, with the pathological findings of diffuse haemangiomas in the liver, skin and pancreas, as has been previously described by Winters, Robinson and Bates (1954) and by Levick and Rubie (1953).

Roentgenological studies are useful in distinguishing hepatic tumours from embryomas of the kidney and neuroblastomas. An intravenous pyelogram is particularly helpful. The kidneys function normally and are usually in normal position in right-sided tumours, although the pelvis and calices may be compressed. Distortion of the pelvis and calices, as seen with a Wilms' tumour, is not present, nor is lateral displacement of the kidney, as with a neuroblastoma, common. The mottled calcification so characteristic of neuroblastoma was not observed, although calcification has been described in some liver tumours. Barium studies of the gastrointestinal tract show displacement of these viscera away from the tumour as one would expect. Downward displacement of the duodenum and hepatic flexure of the colon is seen with neoplasms of the right lobe, in contrast to the forward or medial displacement usually seen with a renal embryoma or neuroblastoma.

Laboratory tests have been of little diagnostic value in these cases. Liver function studies were all essentially normal except in the case of the child with diffuse post-necrotic cirrhosis. Abnormalities in the liver function tests should lead one to question the diagnosis of primary liver tumour. For example, a diagnostic error was made in a newborn infant, admitted at 2 days of age with jaundice and a large epigastric mass. The jaundice persisted as well as other laboratory evidence of disturbed liver function. At operation at 3 weeks of age the mass proved to be a hard, nodular, grey-white 'tumour' occupying the left lobe. Resection of the left lobe was performed and the child recovered without difficulty. However, on microscopical examination this proved to be a large cirrhotic nodule possibly associated with post-intrauterine hepatitis, with marked fibrous tissue proliferation, replacing the normal architecture of the hepatic tissue. The hepatic cells were completely or partially destroyed and showed irregular arrangement. The bile ducts appeared to be increased. It is interesting that the jaundice disappeared within a month after operation and the infant has been perfectly well over a subsequent eight-month period.

Classification

The wide variety of gross and microscopical characteristics of primary liver tumours and the relatively small number of such cases collected at any one institution have made the adoption of a uniform classification difficult (Warvi, 1944; Edmondson, 1956). To add to the problem is the fact that the clinical behaviour is not always correlated with the microscopical appearance, so that a classification based on the pathological data alone appears to be unsatisfactory. For practical reasons it therefore seems appropriate to group these tumours in three broad categories:

1. **Tumours of Hepatic Cell Origin.** This group is made up of all tumours derived from entodermal cells and includes hepatomas, cholangiomas and the cholangiohepatomas. There were no adenomas in this series and the hepatomas have invariably behaved as malignant lesions, although the histological appearance may suggest benignity (Fig. 1a and b).

2. **Tumours of Supporting Structures.** This group comprises those tumours of mesodermal origin including fibromas, haemangiomas, lymphangiomas, fibroangiomas and mesenchymomas. Such neoplasms may be benign, as are most of those in this series, or malignant.

3. **Mixed Tumours and Teratomas.** Such tumours contain cells derived from more than one germ layer. Osteoid tissue, for example, may be seen in liver cell tumours. Teratomas are distinctly rare (Fig. 2).

In this series hepatoma was the most common tumour encountered, occurring in 10 cases. Five were in the right lobe, two in the left and two were centrally positioned. In eight cases symptoms developed in the first two years of life, and the ninth patient had his initial symptoms at 2 years 11 months of age. None of these nine patients had associated cirrhosis so commonly found in adult cases. However, as already mentioned, the tenth case occurred in a 14-year-old girl with post-necrotic cirrhosis of the liver. There were no instances of adenomas or exclusively bile duct tumours among these cases and only a single case of histologically benign cholangiohepatoma occurring in the right lobe of a 10-week-old infant.

Among the tumours of supporting tissue origin were one diffuse haemangioma, two lymphangiomas and one fibroangioma. There were no mesenchymomas, mixed tumours or teratomas. Both

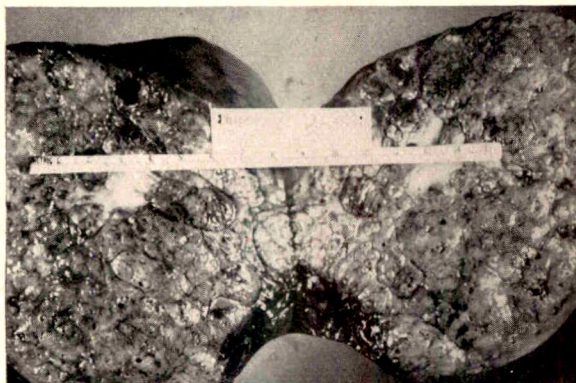


FIG. 1 (a).—Gross and microscopical appearances of a well-differentiated hepatoma of left lobe of liver successfully excised from a 15-month-old infant who subsequently died of undifferentiated hepatic and pulmonary metastases seven months after original resection.

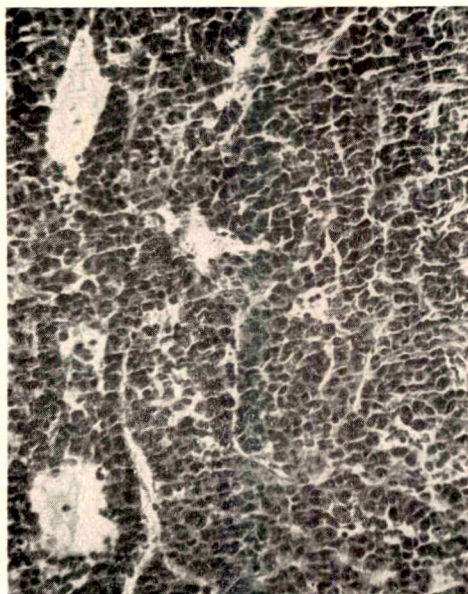
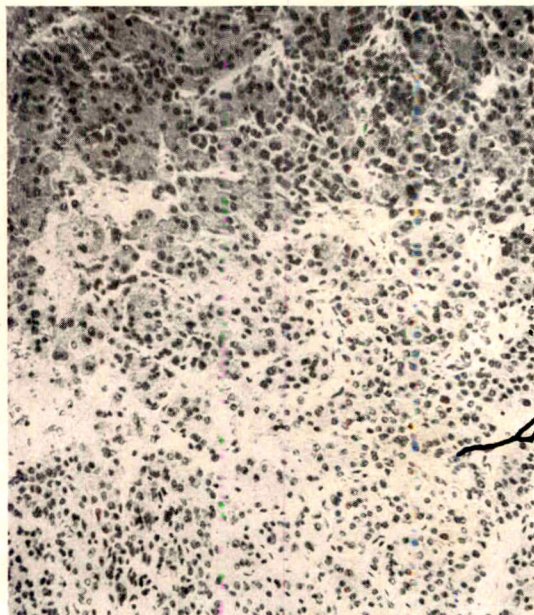


FIG. 1 (b).—Gross and microscopical appearances of a very rapidly growing anaplastic hepatoma of left lobe of liver easily resected with wide margin of normal liver substance in a 2-year-old infant who succumbed to multiple recurrences in right lobe of liver within five months.



FIG. 2.—Gross and microscopical appearances of mixed tumour of liver in a young child; it contained highly undifferentiated hepatoma as well as areas of osteoid tissue.

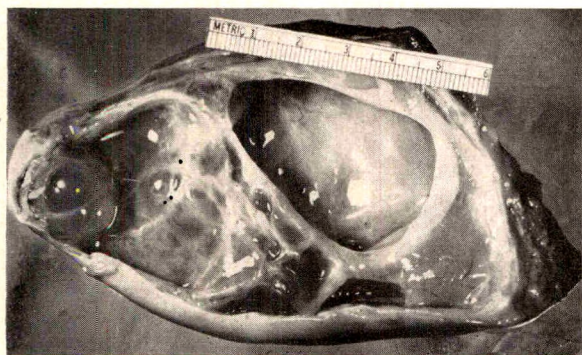
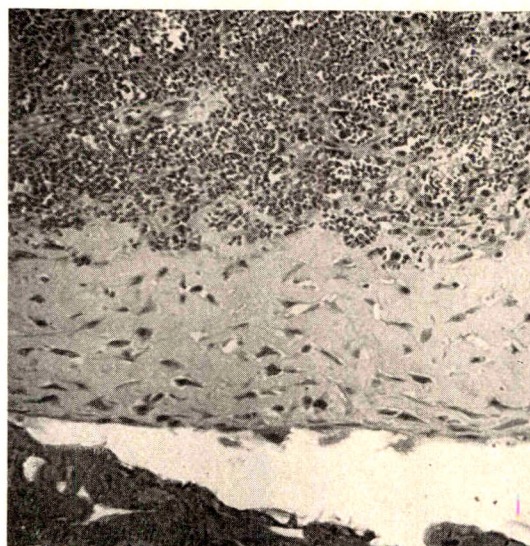


FIG. 3.—Gross and microscopical appearances of a huge rapidly growing lymphangioma involving entire right lobe of liver which was successfully excised from a 9-month-old infant who is well nine months later.



lymphangiomas were found in the right lobe of infants, one 4½ months and the other 9 months of age (Fig. 3). The patient with diffuse haemangiomatosis, already noted, had symptoms at birth. The liver of this patient had numerous small capillary haemangiomas scattered diffusely throughout all portions of the liver parenchyma. The single case of fibroangioma was a newborn infant with the neoplasm originating in the left lobe.

There is a strikingly similar gross appearance of many of these tumours, so that differentiation by this means alone is often quite unreliable. Similarly, the differentiation microscopically of benign and malignant liver cell tumours is occasionally virtually impossible. In one of the hepatomas in this series the cytology and architecture were most suggestive of a benign neoplasm, but the presence of metastases established the malignant nature of the tumour.

Treatment

Effective treatment of primary hepatic neoplasms is at present limited almost entirely to surgical resection. Radiotherapy may be of value in haemangiomas, as suggested by Gross, and in one of our cases of inoperable hepatoma radiotherapy resulted in definite regression in size of the tumour mass. Systemic chemotherapy has not been of value to date.

In tumours limited to either the right or left lobe, surgical removal by total right or left lobectomy is a practical procedure. Such procedures take advantage of the anatomical division of the organ into right and left lobes, each with a largely separate blood supply from the hepatic artery and portal vein. Control of the blood supply and the bile duct system at the hilum of the liver plus similar control of the hepatic veins draining into the inferior vena cava make possible such resections without excessive risk from haemorrhage, air embolism, or bile peritonitis.

In such a procedure for a tumour involving the right lobe the diagnosis is confirmed and operability determined through an abdominal incision. If resection appears possible the abdominal incision is joined or extended by an incision into the right chest through the seventh or eighth intercostal space, and the right diaphragm is divided down to the vena cava. Umbilical tapes are then placed around the inferior vena cava just below the right atrium and above the renal veins. The hilar structures are freed and the appropriate branches of the hepatic artery, portal vein and hepatic duct are carefully identified, ligated and divided. The short hepatic veins from the right lobe to the vena cava are next ligated and divided. This is the most dangerous part of the

procedure since extension of the tumour into this area may not be appreciated until this part of the dissection is under way, and if such extension is encountered there is a considerable risk of haemorrhage or air embolism. The previously placed tapes on the vena cava and control of the hilar structures permit control of such a situation. Following this the liver is transected to the right of the falciform ligament down to the vena cava. During the actual transection the hilar structures are cross-clamped with a Pott's clamp. Interruption of the blood supply by this means can safely be tolerated by the liver for about 15 minutes, and probably longer with the controlled moderate hypothermia (90°-92° F.) customarily employed in these cases. All visible blood vessels and bile ducts are ligated as the dissection proceeds. If the gallbladder is not involved, it may be peeled out of its bed before the transection and used after removal of the lobe for retrograde injection of a methylene blue solution. By this means additional bile ducts can be visualized and ligated. The falciform ligament and posterior peritoneum are used to reperitonealize the raw surface. If this is not sufficient, a layer of compressed Ivalon may be sutured in place to cover the remaining raw area. Penrose drains are placed to drain the right subdiaphragmatic space so that a localized collection of bile or a bile peritonitis will not occur.

The left lobe can be mobilized more easily than the right and this can ordinarily be done through an upper abdominal incision by dividing the peritoneal attachment to the diaphragm and the falciform ligament. It is quite easy to place a row of interlocking mattress sutures just to the left of the falciform ligament and resect the left lobe. It has not been found necessary to perform a hilar dissection or to occlude the hilar structures during this procedure. Again, however, reperitonealization of the raw surface and drainage are important steps.

Results

There have been no long-term survivors in the 10 patients with hepatoma. In one, the diagnosis was not made until post-mortem examination and no treatment was given. In two, only exploration and biopsy were performed, and both died within three months. In two others, exploration and biopsy were followed by radiotherapy. The tumour mass strikingly decreased in size in one of these, but none the less the patient lived only six months after completion of the treatment. The other lived only four months after therapy.

Right lobectomy was performed in four patients and there were three early deaths. One of these

patients died from operative haemorrhage, and a second from haemorrhage and air embolism. A third unfortunate death resulted from staphylococcal peritonitis and septicaemia two weeks after operation and at autopsy no tumour was found. All three deaths must be considered preventable. The first two cases were in retrospect inoperable because of tumour invasion across the midline posteriorly in the area of the hepatic veins. The third death presumably followed contamination in the operating room or via the drain site. The fourth patient who had a resection of the right lobe died at home two and a half months after operation following a brief acute illness suggestive of intestinal obstruction. The patient was not returned to the hospital during this illness and no autopsy was performed. A left lobectomy was performed in the final patient, and he died with massive metastases in the right lobe seven months after resection. This last patient had been known by his parents to have an abdominal lump since 3 months of age, but no treatment was sought until 15 months later at which time a huge tumour in the left lobe was found.

The single patient with a cholangio-hepatoma had a resection of the right lobe of the liver at 10 weeks of age (Fig. 4). He is living and well 12 months later with no evidence of recurrence.

Both patients with giant lymphangiomas had tumours occupying almost all of the right lobe. Resections of the right lobe were done at 5 and 9 months, and both patients are in good health



FIG. 4.—A 10-week-old infant one week after total right hepatectomy for cholangio-hepatoma.

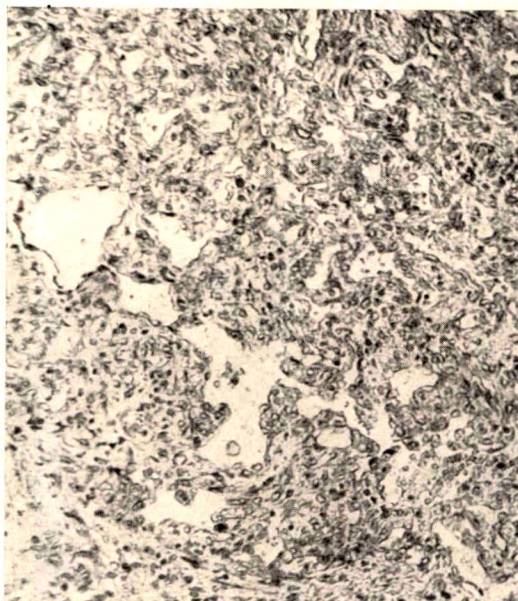


FIG. 5.—Microscopical appearance of liver removed at autopsy from an 8-week-old infant with multiple diffuse haemangiomas who had been under treatment since birth for 'heart failure'.

six and a half years and nine months later. The infant with a fibroangioma of the left lobe had a left hepatectomy at 3 weeks of age, and is well 14 months later.

None of the long-term survivors after resection of the right or left lobe shows any evidence of impairment of liver function. Although in all cases there was a plateau in weight gain for a few weeks after operation, subsequent growth and development patterns have been entirely normal.

The patient with diffuse haemangiomas of the liver, as well as of the pancreas and skin, was treated for heart failure from birth and died at 8 weeks of age. The diagnosis was made from the autopsy findings (Fig. 5).

Discussion

Primary liver tumours are not rare paediatric problems. Without treatment the prognosis is poor in both the malignant and benign varieties, as indicated by the larger reported series (Andersen, 1951; Gross, 1953; Lee, Newstedt and Siddall, 1956). With adequate surgical resection the prognosis in cases of benign tumours is good, and after such treatment normal growth and freedom from liver impairment may be expected. The outlook for patients with malignant tumours, even after operation, has thus far been poor, but with the

development of more adequate techniques in achieving wide resections there is reason to believe that success may be achieved. One remarkable exception is the case reported by Lee *et al.* (1956) of an infant with a huge hepatoma confirmed by biopsy. No treatment was given but spontaneous regression occurred and the child was reported in good health 10 years later.

Establishing a clinical diagnosis of a primary liver tumour is ordinarily not difficult; however, the differentiation of a benign from a malignant tumour clinically or at operation may be quite impossible. Two such dilemmas occurred in this series. Since surgical excision currently affords the only chance of eradicating such lesions, it is our opinion that in the absence of distant metastases isolated lesions should be removed.

The techniques of resection of either the right or the left lobe are sufficiently well developed to permit their application with a reasonable assurance of success. The major problems are haemorrhage, air embolism and bile peritonitis. An anatomical technique with control of the afferent and efferent blood supply, controlled hypothermia, reperitonealization of the cut surface and adequate drainage are methods which contribute to the success of these procedures.

Summary

The majority of primary liver tumours which present as clinical problems in children are malignant and occur in the first two years of life. Such tumours develop in a normal liver, and are not superimposed on a cirrhotic process as in adults.

From the practical standpoint these neoplasms can be classified as (1) tumours derived from liver cells, (2) tumours derived from supporting cells,

and (3) mixed tumours. Those derived from liver cells are malignant in the vast majority of cases, although the microscopical picture of some is quite benign.

The solid tumours of the liver should be treated in a uniform manner, adequate surgical excision through normal liver tissues being the best available procedure.

A surgical technique based on sound anatomical principles and planned to minimize the risks of haemorrhage, air embolism and bile peritonitis makes removal of these tumours by a resection of either the right or left hepatic lobes a logical and practical procedure.

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RESULTS WITH ABDOMINAL RESECTION IN HIRSCHSPRUNG'S DISEASE*

BY

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For six years we have been practising abdominal resection for Hirschsprung's disease. The method is also known as segmental resection, anterior resection or State operation.

The operative technique has, apart from certain small alterations, always remained the same. In the application of this procedure certain aspects have been revealed which are important for the theoretical interpretation of the disease and also have practical significance, no matter which method is considered the best.

We need not go into the fundamental work of Swenson and Bodian. Swenson himself presented his views in detail five years ago at the first meeting of the British Association of Paediatric Surgeons, and Ehrenpreis (1955) lectured on Hirschsprung's disease in the newborn infant at the same time.

In 1951 and 1952 we operated on our first cases according to Swenson's method (Swenson and Bill, 1948) and it occurred to us at that time that a dissection of the rectum might possibly lead to a disturbance of sexual potency, to incontinence and to disturbances in evacuation of the bladder. For this reason we switched to the State operation in 1953. Meanwhile it has been proved that this anxiety was unfounded. Swenson (1957) reported that eight patients who had been treated surgically had become fathers and that six others, all over 20, had no disturbance of potency. Wyllie (1957) reported that, among the large number of patients from the Great Ormond Street Hospital, hardly any lasting disturbances of bladder function had been observed. Incontinence of faeces usually disappears after some time. Only Hiatt (1958b) reports lasting troubles in 16%. Injury to the pelvic vegetative nerves can however only be avoided if the dissection of the rectum is made close to the wall of the bowel. As Swenson himself says, this part of the operation is time-consuming and difficult. But

this difficulty disappears when the intra-abdominal method is used. Thus it is simpler and can easily be withstood by weak infants. Only the simplicity of this procedure therefore induces us to keep on using it.

Fig. 1 shows that the majority of cases were operated on between the ages of 6 and 12 months.

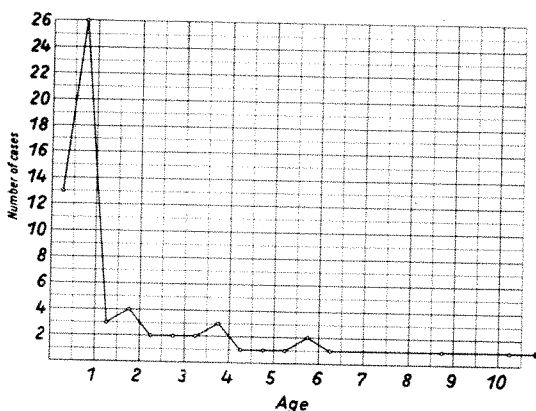


FIG. 1.—Age (yr.) of children at time of operation.

From 1953 to 1958, 67 children were operated on in this way. In 56 cases there was the typical finding of a narrow segment.

In 11 cases there was no narrow segment. These cases belong to the megarectum group. Pathological examination disclosed absence of ganglion cells at the lower portion of the resected bowel.

In 60 of the 67 cases treated surgically the diagnosis was confirmed histologically. In seven cases there was no complete aganglionosis. Besides large nerve trunks occasional ganglion cells were found throughout various sections of the lower end of the specimen. We took these cases to be Hirschsprung's disease also.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

Operative Technique

In abdominal resection the upper rectum is cut through. The resection either involves the sigmoid alone or more often extends to the splenic flexure. In 1952 State pointed out that in most cases the rectum, although aganglionic, is wide or at least distensible. In dissection of the upper rectum it can very often be seen how the narrow segment becomes somewhat wider in the lower direction. The level of the transection is about 1 cm. below the pelvic peritoneal floor (Fig. 2). This level is still easy to reach from an abdominal incision. The distance of the anastomosis from the anus varies according to

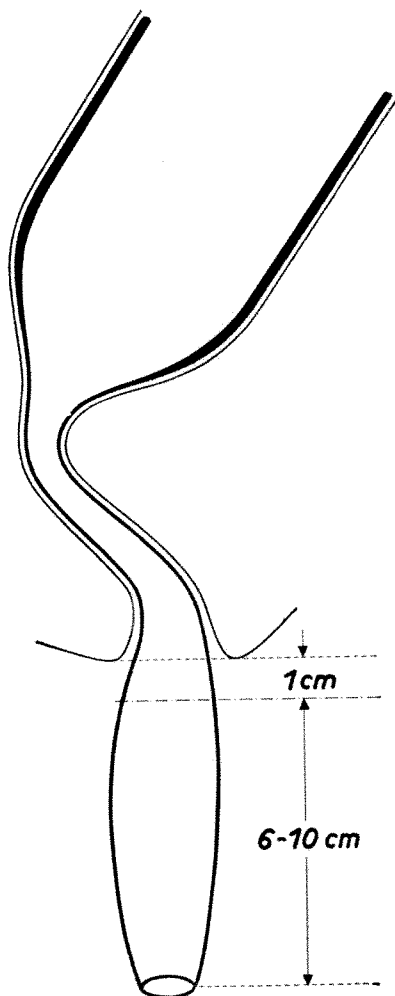


FIG. 2.—Level of transection is situated in upper rectum 1 cm. below pelvic peritoneal floor. Distance from anus varies from 6-10 cm.

the age of the child, and the peritoneal floor is sometimes lower, sometimes a little higher. It is about 6-10 cm. and can always be touched by the finger. The whole sigmoid at least must be removed. The wide lumen and the hypertrophied wall are not suitable for anastomosis. In addition resection of the sigmoid eliminates a reservoir in which faeces can accumulate. When the dilatation extends into the descending colon, we have resected as high as the splenic flexure. Even when the resection is extended to the splenic flexure, both lumina are not usually the same size, but the wall is no longer hypertrophic. Care must be taken in anastomosis to ensure that the surplus of the wide lumen is evenly distributed over the narrow lumen (Fig. 3). In the few Hirschsprung cases which had a wide aganglionic rectum but no narrow segment the problem was reversed. We always perform the anastomosis with an open bowel without clamps. A slight soiling of the operational area cannot always be avoided; breakdown of the suture, infection or peritonitis have never occurred. In a large number of cases the anastomosis remains wide and can only be felt as a fine scar. The colon and rectum eventually attain the same calibre. In other cases a slight sickle-shaped projection exists to one side or all round. Occasionally a moderate or serious stenosis has occurred. Then part of the evacuation pressure is lost. But for the success of the operation it is conditional that the anastomosis is wide.

Achalasia

In one of the first cases which was operated on in this way five years ago abdominal distension and constipation recurred two years later (Fig. 4). Examination revealed that there was no stenosis of the suture. The remaining rectum had expanded. The ampulla was filled with soft faeces. After a vigorous sphincter dilatation and washouts, evacuation started again and the abdominal dilatation disappeared. This child has had no stool difficulties for three years.

It is very interesting that Thomas (1958) describes the same findings in two cases treated by recto-sigmoidectomy. This observation, which we also made in other children, is important and suggests that in a case of so-called recurrence the cause is a disturbance of anal function, of the evacuation reflex. Probably it is impossible for the sphincter to relax, in other words an achalasia; or, instead of a relaxation, a contraction occurs. This disturbance of co-ordination must already exist before the operation. But as long as there is a narrow segment this disturbance does not appear so clearly, as it is concealed by the narrow segment. It may be

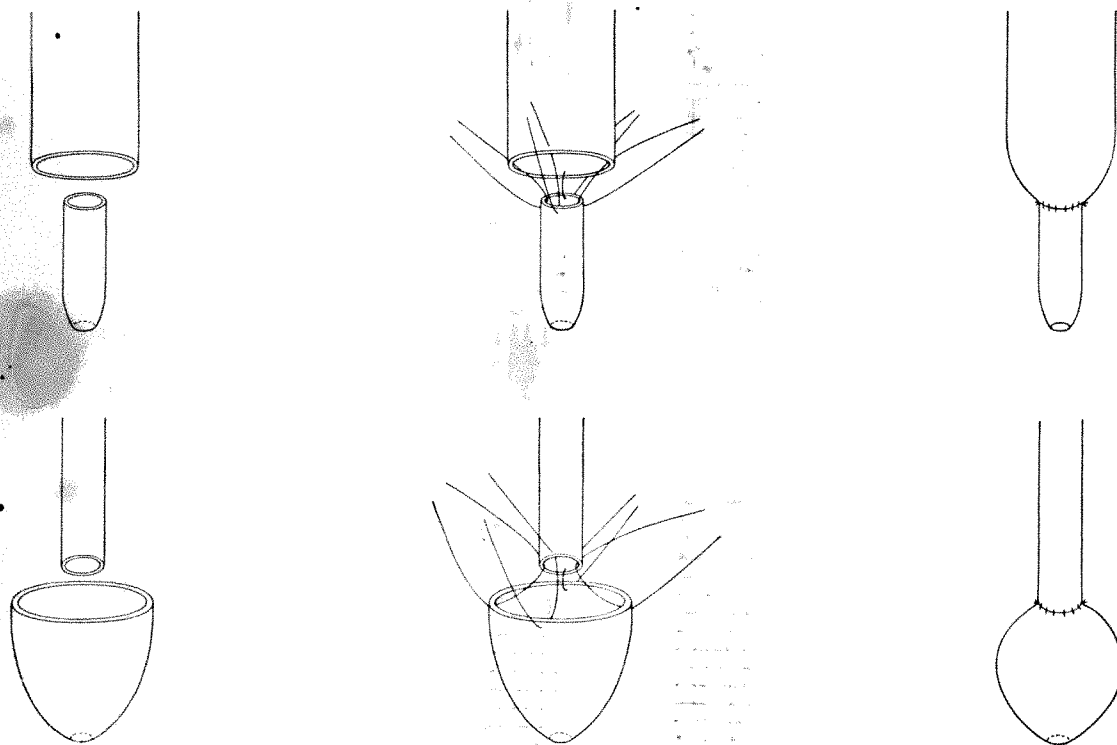


FIG. 3.—Great difference of calibre in common form of Hirschsprung's disease (above), and in megarectum type (below), causes difficulties in anastomosing technique. Surplus of wide lumen must be evenly distributed over narrow lumen.

assumed that this disturbance of co-ordination is part of the whole disease and is also an expression of the defect of the parasympathetic nerve system of the pelvis. This theory of achalasia is an old one. In 1934 Hurst proposed to treat Hirschsprung's disease by dilating the sphincter. The result must however have been poor since nothing was known at that time of the importance of the narrow segment. Dilatation causes rupture of muscle fibres. The strong sphincter closure is weakened and evacuation made easier. The weakening of the sphincter is intended to replace the active relaxation which is lacking. With abdominal pressure the weakened sphincter is overcome passively during defaecation. As we must assume that this achalasia exists in every case of Hirschsprung's disease, we dilated the sphincter immediately after every operation. It soon appeared that the desired effect was not permanent in some cases, especially in infants. Apparently the severity of achalasia varies with different cases. The dilatation had to be repeated several times. From later examinations we ascertained that a powerful sphincter closure had often reappeared. Lasting incontinence has never occurred.

Immediate Post-operative Results

Most children began to empty their bowels one or two days after the operation and no further measures were necessary. Other cases had to be helped from the start with a flatus tube and enema and it was a long time before they could evacuate on their own. The abdomen became again distended. A tube or the finger need be inserted only a few centimetres and gas and stool are evacuated and the abdomen collapses. Here we are dealing mainly with infants. The colon appears to have no power at all to propel stool in such cases and the slack abdominal walls cannot effect defaecation. But it also happens that, after easy emptying at first, difficulties arise because the anastomosis has a tendency to narrow. These difficulties can be surmounted if daily bouginage with very thick bougies is begun soon after the operation. Thus one can avoid stenosis of the suture and at the same time maintain the effect of sphincter dilatation.

Later Results

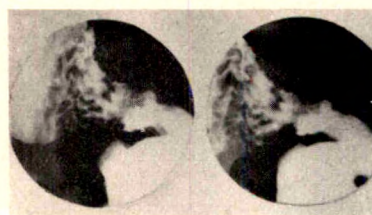
Six of the children on whom we operated died. All were infants. Five deaths had no immediate



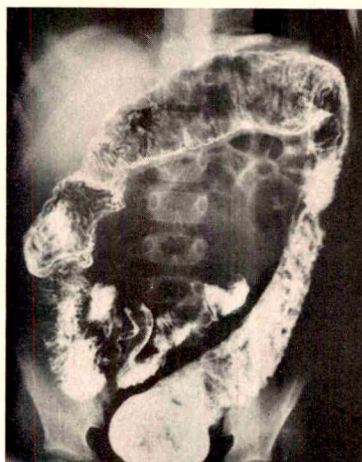
(a)



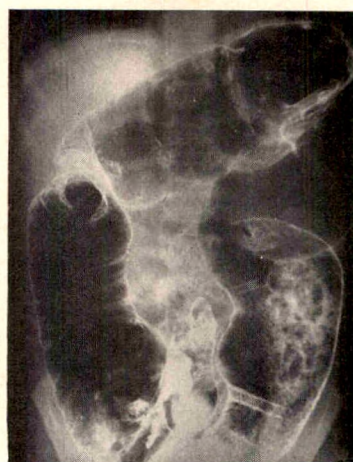
(b)



(c)



(d)



(e)

FIG. 4.—8-year-old girl with signs typical of Hirschsprung's disease (*a-c*) operated on five years ago; recurrence of symptoms two years after operation (*d, e*). Considerable dilatation of large bowel. Remaining rectum wide.

connexion with the operation. One of the first children died of peritonitis; perforation of the bowel had been caused by bouginage. Another child was found dead in bed at home. The third child died during an operation on an incisional hernia in another hospital. The next died also at home, probably as a result of ileus. Another, in whom a colostomy had been done in the newborn period, died during closure of the colostomy. Only one child died two days after the resection, a 6-month-old infant with mongolism.

We have examined many of the children since the operation or received written reports from their parents. Children who have been operated on this year have not been taken into consideration. We have only been able to examine a certain number radiographically. We think, however, that they will suffice to give a picture of the results (Figs. 5-7).

Thirty-seven of the 67 children have been completely relieved of their symptoms (Table 1), they

TABLE I
RESULTS OF ABDOMINAL RESECTION IN 67 CHILDREN
WITH HIRSCHSPRUNG'S DISEASE

Year	No. of Cases	Laxative, Enema, Abdominal Distension			Died	No Response
		None	Sometimes	Always		
1953-58	67	37	11	9	6	4

need neither enema nor laxatives, they have no abdominal distension and have bowel movements daily. Nine results were poor. The 11 children who are listed in the second group need laxatives and enema occasionally*. A few sometimes show slight abdominal distension. Of course it would still be possible to record a few of these children as good results. Sixteen children empty the bowels once a day; the remaining children do this two or three times daily. Only in some of the cases are the motions solid; usually they are loose. With some children, who had initial difficulties in evacuation, the results have improved with the course of time, whilst others deteriorated some months or even as much as two years after the operation. It may be assumed that from approximately the third year after the operation the results remain steady. It is remarkable that even cases which are clinically completely free of symptoms and seem to be cured still show a certain dilatation of the colon. Wyllie (1957) made the same observation in his children after rectosigmoidectomy. Usually one can still detect the site of anastomosis fairly clearly. The rectum is distended. Cases with noticeable dilata-

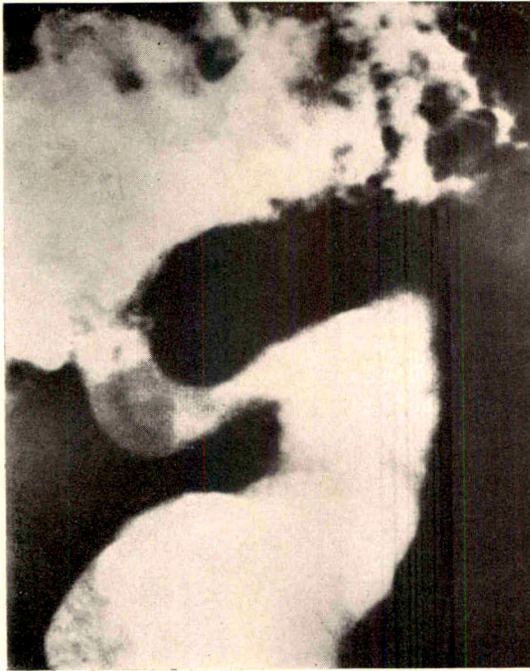
tion can also be free of symptoms. The distended bowel is in the stage of compensation. This stage of compensation can last for years and is then practically equivalent to a cure, although the latent possibility of a deterioration or a slow retention of stool may exist in some cases.

Discussion

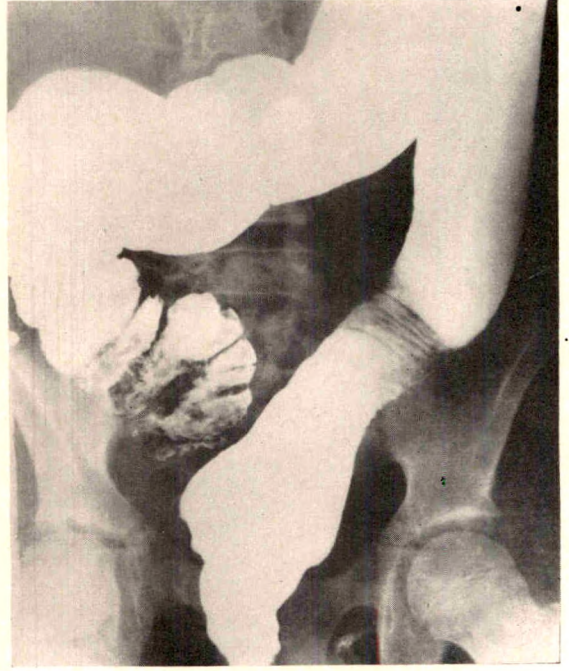
Not all cases are equally suitable for abdominal resection. The narrow segment can be situated deep in the rectum, and then anastomosis becomes difficult or impossible; or the narrow segment extends deep into the rectum. In the commonest forms of Hirschsprung's disease, however, when the narrow segment is situated in the rectosigmoid, abdominal resection can achieve good results. The most important thing for the success of the operation is that no obstacles to emptying should remain. No anastomotic stenosis must exist, nor any hindrance to evacuation because of a closure of the anus or a diminished ability to open. None of the narrow segment must be left, but most of the aganglionic rectum must remain. Because on radiological and rectal examination after the operation the rectum is wide, or at least distensible, we cannot believe that the remaining rectum is the cause of any failure. It is not a passive hindrance as is the narrow segment. If evacuation troubles occur, then the sphincter is responsible. Therefore, from this point of view also, a second operation is not necessary.

In rectosigmoidectomy, transitory disturbances of continence occasionally appear as the reports of Swenson (1957), Hiatt (1958a), Wyllie (1957) and others show. This perhaps leads to the conclusion that with dissection of the rectum the achalasia of the sphincter is removed at the same time. A transitory disturbance of continence seems especially favourable with regard to final success. If the bowel can empty itself immediately without any hindrance in the post-operative phase, it has the opportunity to return to normal calibre and is not open to the danger of renewed dilatation. We know that it can return to normal calibre from the colostomy alone. If the sphincter then gradually regains its ability to close, the colon has time to adapt itself functionally to the sphincter. The question of a lasting weakening of the sphincter seems to be the problem with abdominal resection. The function of the sphincter must be permanently weakened so far that continence is just retained. A single dilatation of the sphincter can effect this. But the sphincter has a tendency to regain its ability to close tightly. If that happens, the dilatation must be repeated and it is necessary to continue treatment for some time with

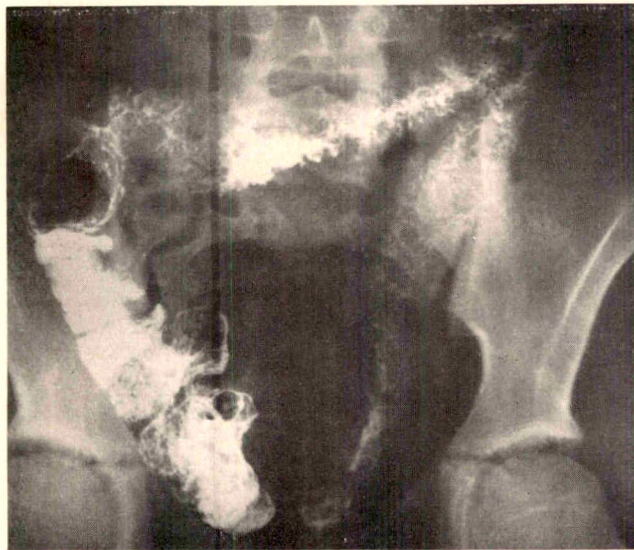
* Ten of these 20 cases have subsequently become symptom free.



(a)



(b)



(c)

FIG. 5.—X-ray (a) before, and (b, c) six months after operation on a 19-year-old boy. Large bowel completely filled and showing good emptying. Operation performed five years ago. Full relief of symptoms.

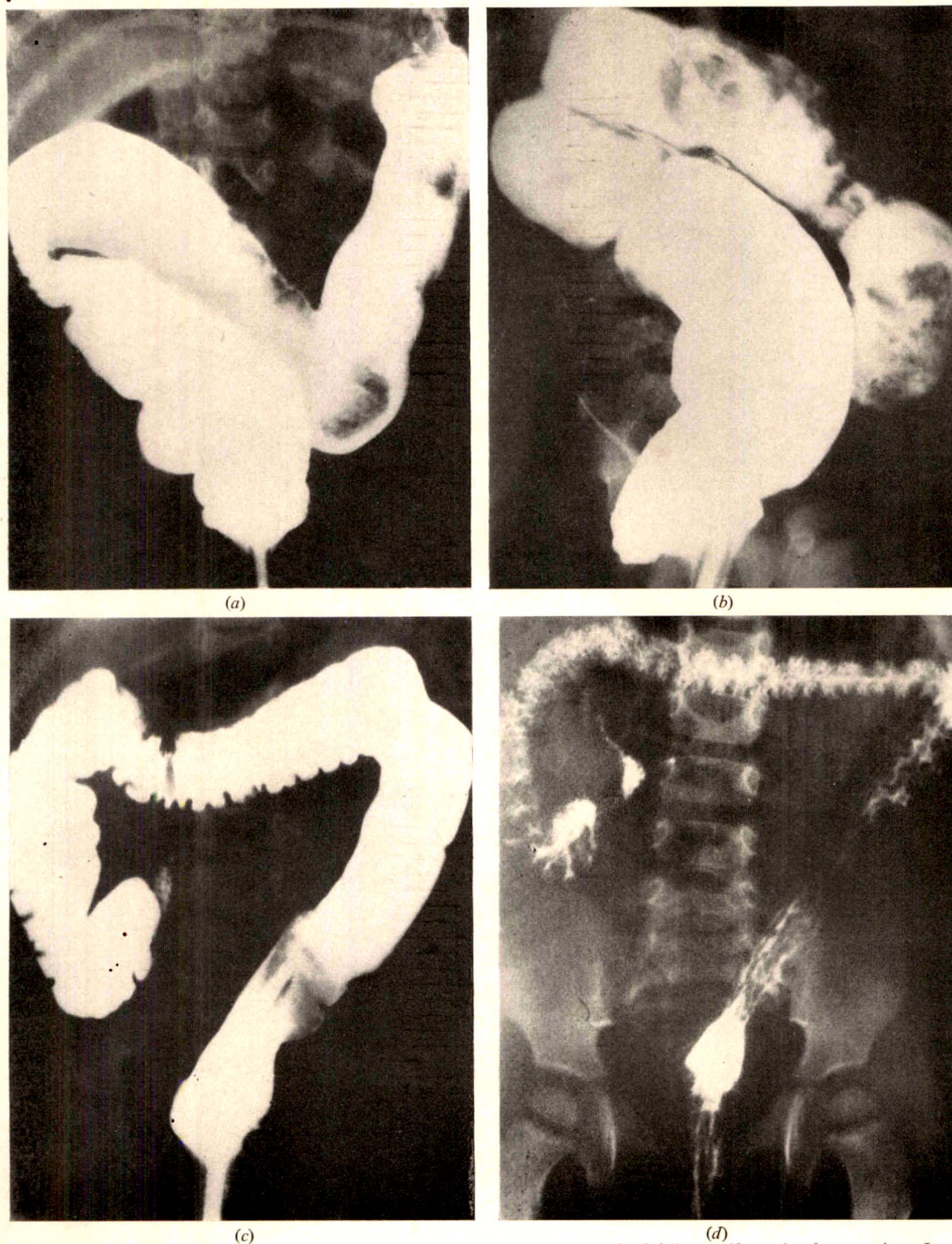


FIG. 6.—(a, b) X-rays of an infant with megarectum type of Hirschsprung's disease; (c, d) follow-up 12 months after operation. Level of anastomosis can be seen. Good emptying.

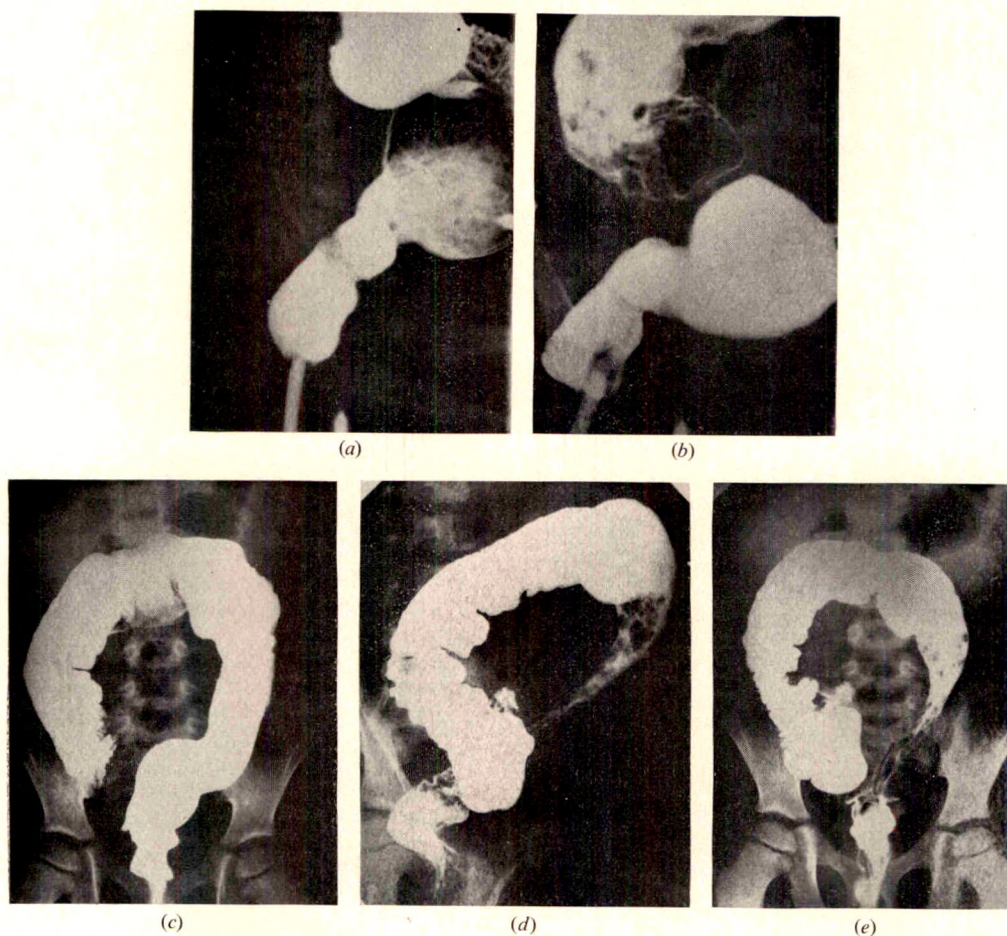


FIG. 7.—5-year-old boy operated on at 6 months of age. X-rays (a, b) before, and (c-e) four years after operation. Ascending and transverse colon a little more distensible than normal. Satisfactory evacuation of descending colon. Slight diverticula in region of anastomosis. Full relief of symptoms.

thick bougies. The reason why deterioration has been noticed in some of our patients since our 1958 publication (Rehbein, 1958) is to be found in the fact that this systematic treatment, the necessity for which Wyllie (1957) has also pointed out, has not been sufficiently carried out. Up to now this treatment has given us good results in children in whom the earlier results had deteriorated. We may therefore assume that for the other children in the second and third groups of the Table there is still the prospect of a cure. The passage from a good result to renewed constipation can be insidious and unnoticed. If, for example, the emptying of stool no longer takes place daily, or a slight abdominal distension is observed, or even if stool and gas have to be evacuated with the tube from time to time, that is a sign that the bowel is threatening to enter the stage

of decompensation. It is necessary to act on these signs in good time.

One must as a rule seek the cause of evacuation difficulties in the anastomosis or in the anus. Only once were we induced to remove the dilated descending colon in an infant during a second operation three months after resection of the sigmoid. The result was good (Fig. 8). In many cases we have resected the colon to the splenic flexure at the beginning. But we are not sure whether that is always necessary. If evacuation cannot take place unhindered, it is of no use however high the resection is.

The treatment of Hirschsprung's disease is most problematical in infancy, but most children are treated at that age. Swenson has for some years limited himself to making a colostomy in infants and

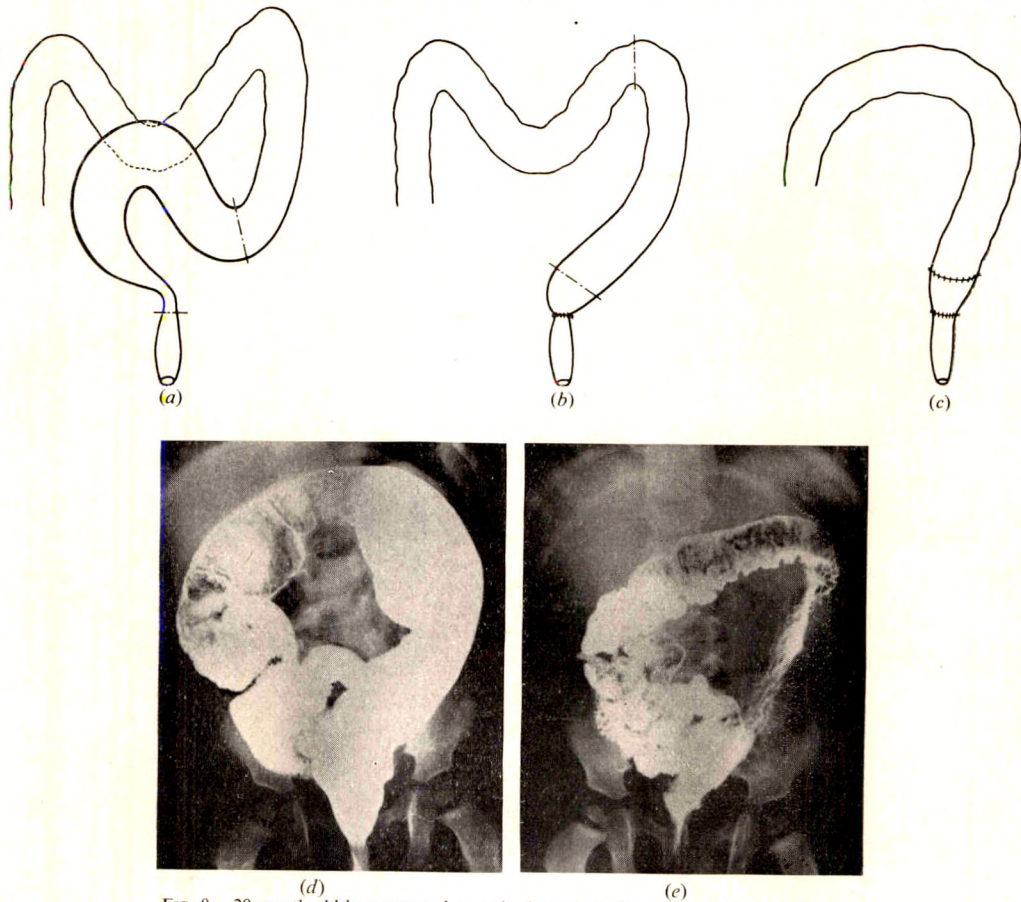


FIG. 8.—20-month-old boy operated on twice in period of three months. (a-c) diagrams of procedure; (d, e) X-rays seven months after last operation. Free of symptoms.

delaying the resection until the children are 12-18 months old. We have always performed the resection in the first year, and only with ileus in the first weeks of life have we done a colostomy. The future must show which is the better way. But it is the general opinion that operative treatment must take place in infancy. On the other hand, by this early treatment we also receive the serious cases which would have died earlier. So it must be explained that post-operative treatment is more necessary than in older children. In addition these children do not know normal bowel evacuation and do not use abdominal pressure. Stool simply remains in the terminal bowel. One can only treat with the tube, enema, bouginage and laxatives until they have learned spontaneous emptying. If the children are a little older they can help themselves and one can execute bowel training.

We have intentionally indicated the difficulties connected with the application of abdominal re-

section. The procedure is smaller and simpler than rectosigmoidectomy but demands intensive post-operative supervision of the child to a higher degree. It is certainly too early for a final picture to be drawn up. The arguments which are raised against the method are not justified in so far as failure lies not in the method but probably in insufficient post-operative treatment. The recurrent necessity for this treatment is a disadvantage compared with rectosigmoidectomy. These difficulties are not insuperable and therefore we see at the moment no reason to depart from this method.

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A NEW OPERATION FOR THE TREATMENT OF HIRSCHSPRUNG'S DISEASE*

BY

BERNARD DUHAMEL

From Paris

The excision of the aganglionic segment of the recto-sigmoid colon proposed by Swenson is the logical outcome of the new conception of the aetiology of Hirschsprung's disease and I do not think it necessary to discuss it here any further.

The operation which I shall describe constitutes but a technical variance of Swenson's operation and is not a new method; it has also some other applications apart from the treatment of congenital megacolon. The object of this operation is to exclude and not to resect the malformed rectum and all dissection of the pelvis is avoided. The functionally healthy proximal colon is brought down to the margin of the anus in a plane of anatomical cleavage, and thus the nervous system of the bladder and neuro-muscular apparatus of the sphincters are preserved *in toto*. A wide anastomosis between the colon and the excluded rectum is performed and, by preserving the rectum, an important area of reflex activity is preserved.

Hirschsprung's disease is a serious condition but it is not a malignant disease in the usual sense of the term; therefore an operation designed to remedy the condition should not be of excessive severity, and there should be no risk that one functional anomaly (urinary incontinence or impotence) will be substituted for another. Swenson's operation is a delicate and difficult intervention which only gives excellent results if it is carried out by a very competent surgeon operating on children of a certain age.

Since the characteristic deficiency of ganglia in Hirschsprung's disease nearly always affects the whole of the rectum down to the level of the internal sphincter, an extensive resection of the rectum, which is associated with considerable shock, especially in the newly born, must be performed in order to obtain a satisfactory surgical result.

Dissection of the rectum can be carried out close to the muscular layer since one is not dealing with a malignant condition; it is nevertheless possible to traumatize the pelvic nervous plexus supplying

the bladder or the genitals. Complete ablation of the mucous membranes of the rectum or of its nerve supply will interfere with rectal sensation which is indispensable to the perfect function of the sphincters.

Whatever the extent of the resection of the rectum, it is always incomplete inferiorly as it is essential to preserve the rectal sphincter. Thus an unsatisfactory result is common and relapses are possible.

The end-to-end anastomosis is liable to separate either partially or completely if the vitality of the pulled-down colon is endangered or if the operative technique is incorrect. In a certain number of cases serious complications, such as peritonitis, pelvic abscess or fistula, may result.

Lastly the anastomosis can (and this is a most frequent complication) become stenosed and may at times become completely occluded.

It is because of these complications, which cannot be avoided in spite of the technical modifications described by some authors, that some surgeons have rejected Swenson's operation and returned to abdominal resection followed by dilatation of the sphincter. This is probably a retrograde step since one knows that in most cases the lower part of the rectum and the internal sphincter are themselves malformed. The same objections could be raised against those who have proposed a recto-sigmoid-myotomy inspired by the operation of Heller since they do not prolong their extramucous incision beyond the level of the pouch of Douglas, and have to complete the operation by carrying out an anal dilatation.

In a recent book (Duhamel, 1957) I have described and illustrated in detail my surgical technique and I shall therefore mention here only the essential steps.

Operative Procedure

Abdominal Approach. (1) The rectum is divided, closed and buried at the level of the pouch of Douglas, as in Hartman's operation.

(2) After resection of the narrowed recto-sigmoidal zone and that of the adjoining megacolic

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

segment, which is usually toneless and full of faecoliths, the proximal colon is mobilized (care being taken to preserve its blood supply) and must be long enough to allow its being brought down to the anus; its lower end is temporarily closed using a few large sutures.

(3) The cellular retro-rectal space is now opened by cutting through the meso-rectum and dissection is carried downwards in the midline using the finger, the hand or a swab on a holder until the level of the pelvic diaphragm is reached.

Perineal Approach. (4) The anus is dilated and an incision is made along its posterior circumference at the line of the ano-cutaneous junction. The wall of the anal canal is then dissected off the external sphincter and after a few muscle fibres have been split longitudinally at the upper border of the external sphincter one meets the retro-rectal dissection of the abdominal approach.

(5) With the aid of a curved clamp introduced through this opening, the resected lower end of the colon is grasped and pulled down to the level of the skin incision. The lower end of the colon is reopened and its posterior margin is sutured to the posterior cutaneous lip of the retro-anal incision.

(6) Two Kocher's forceps are inserted, one blade into the lower colon, the other into the rectum; their points meet in a V high up in the bowel and their bases are held apart so that they come to lie at the lateral angle of the colon and anus. The forceps are tightened and then tied together. The colon cannot now retract and the forceps produce haemostasis. After a few days a longitudinal enterostomy opening between the colon and the rectum is produced. The newly fashioned rectum has an anterior part which is aganglionic, reflex control of defaecation thus being assured, and a posterior part composed of colon which will ensure mobility.

I have operated on 11 cases of Hirschsprung's disease using this technique; this is obviously too small a series for statistical purposes but I know that some French, Spanish, Finnish and Swiss surgeons have adopted this operation with results similar to mine. In every case we have been struck by a complete absence of operative shock and by the fact that spontaneous stools are passed within two to four days. Cutting out of the enterostomy forceps takes about a week followed by scarring without com-

plications. The functional result has always been perfect and radiological studies have shown complete regression of colonic dilatation and a normal diameter after an interval of about two to four months.

All these cases show an improvement as good as those operated on by Swenson's method, but I realize that this alone will not convince experienced surgeons who are anyway getting regularly satisfactory results. There are however two particular aspects of the operation which I think constitute a distinct improvement on the old technique. Firstly, this operation is the only one which allows re-operation on cases of 'failed' Swenson's operation, both in failures due to insufficient resection of the lower segment and in those with stenosis of the anastomosis. This advantage has already been recognized by numerous surgeons. Secondly, the most important advantage of the operation is that it allows a considerable lowering of the age limit at operation. Most authors agree that Swenson's operation is dangerous in the newly born because of the difficulties encountered in dissecting the rectum at that age. Swenson himself advises against recto-sigmoidectomy until the child is at least 12 to 18 months old, and suggests that, if necessary, a temporary colostomy only should be carried out.

When recto-sigmoidectomy is performed during the first months of life, the results are often unsatisfactory because in order to save a sufficient amount of gut for proper function of the anal reflexes one is forced to preserve too much of the internal sphincter and it is often necessary to perform a complementary sphincterotomy. The technique that I have described overcomes these disadvantages. I have operated on eight children of less than 6 months of age, five of whom were less than 3 months old, and I have noticed that the younger the child the better have been the operative results and the quicker the return to normal function. Realizing the particular seriousness of congenital megacolon in the neonatal period, and the dangers of a temporary colostomy at this age, we believe that the introduction of a curative operation for Hirschsprung's disease in infancy will allow us to save more children suffering from the so-called 'malignant' form of the disease in the neo-natal period.

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INTESTINAL OBSTRUCTION IN THE NEWBORN INFANT*

BY

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The syndrome known as mechanical ileus or intestinal obstruction is a many-sided problem, the solution of which, in childhood and especially in the newborn infant, is one of the most difficult tasks of the paediatric surgeon, as regards both diagnosis and treatment.

The diagnostic difficulties are due above all to the fact that just at this age the pathological changes causing intestinal obstruction are so numerous. As intestinal obstruction is no more than a symptom, the physician diagnosing it is at most half way to recognition of the disease. The site and type of obstruction are not as yet clear.

The difficulties in treatment arise from the fact that ileus is not only a local affection but also a grave general disease in which quick decisions must be made.

Clinical Features

The clinical picture depends essentially on three factors: on the level of the obstruction, on its duration and on whether it is complete or partial. In high-seated obstruction vomiting is one of the first signs and abdominal distension is limited to the epigastrium. In low-seated obstruction distension of the whole abdomen precedes vomiting. In the newborn infant swallowed air reaches the rectum only after 12-24 hours. Therefore if the obstruction is at a low level, abdominal distension will rarely be present before 12 hours have elapsed. On the other hand, it should be remembered that meteorism during the first 12-36 hours of life may be physiological. In partial obstruction, such as congenital stenosis of the intestine, vomiting is the first and most striking symptom, while abdominal distension may be minimal because the intestinal air is able to pass through the stenosis.

Investigation of bowel function in the first days of life, that is to say the presence or absence of meconium, may provide important clues in the diagnosis of intestinal obstruction, although no hard

and fast rules exist in this respect. Delayed passage of meconium should always lead one to suspect low intestinal obstruction, such as atresia of the rectum or colon, meconium ileus or Hirschsprung's disease, although this symptom may also occur in normal babies. On the other hand, evacuation of meconium does not exclude a primary high-seated intestinal obstruction, since meconium is produced in all parts of the intestinal tract and bile pigments reach the intestine by way of the blood.

Microscopical examination of the meconium for cornified epithelial cells and lanugo hairs makes it possible to distinguish between cases with early primary obstruction of the intestine and those in which the obstruction developed later in foetal life by strangulation, volvulus or intussusception. In primary congenital atresia of the bowel these meconium elements are absent.

Radiology

Radiological findings are of prime importance in diagnosis. In every case of ileus in the newborn infant radiological examination in the upright position is called for. Plain films are important since conclusions may be reached as to the site of the obstruction from the number and position of distended loops and fluid levels. In duodenal obstruction the radiological picture is typical. It shows a dilatation of the stomach and only one pathological fluid level on the right of the spine (Fig. 1). The corresponding finding at operation in such a case is seen in Fig. 2. The superior segment of the duodenum is greatly distended and as large as the stomach. In lower intestinal obstruction a plain film in the upright position reveals multiple distended loops and fluid levels (Fig. 3).

Furthermore, an enema with a contrast medium should in no case be omitted, as in newborn babies it is often impossible to decide whether the distended loops belong to the small bowel or to the colon. Such a procedure also provides valuable information as to the permeability and calibre of the colon and the site of the proximal colon. It may thus reveal

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

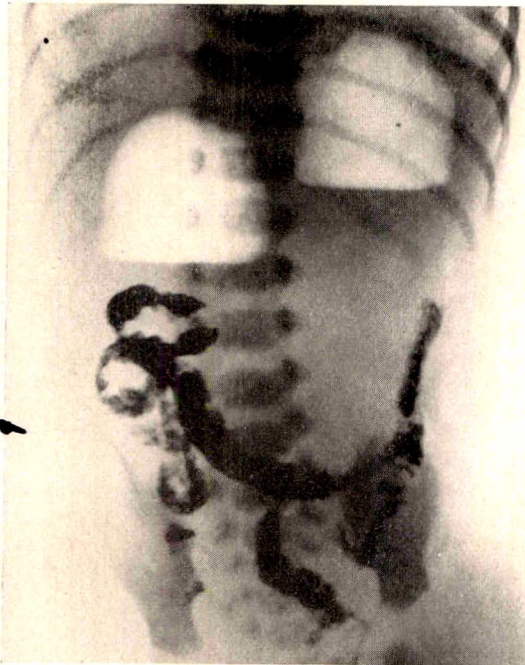


FIG. 1.—Duodenal atresia in a 5-day-old infant.

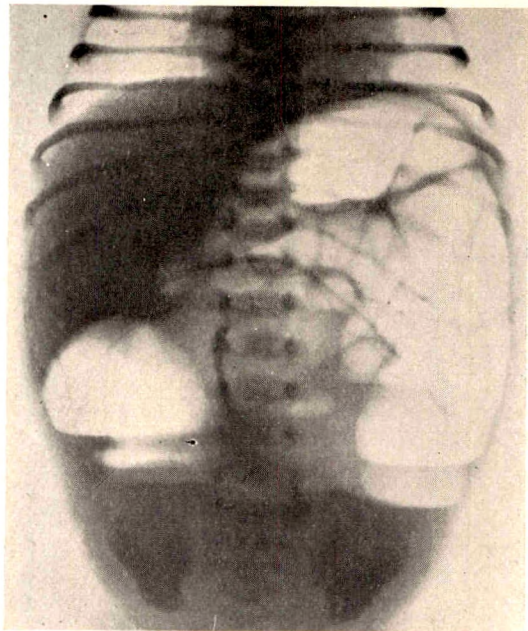


FIG. 3.—Multiple distended loops and fluid levels in lower intestinal obstruction.

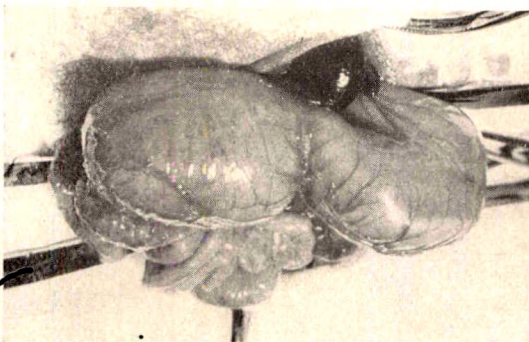


FIG. 2.—Operative findings in duodenal atresia. Greatly dilated superior segment of duodenum.

the presence of atresia, Hirschsprung's disease or malrotation.

Barium is generally used for contrast enema, but the use of resorbable preparations, such as Ioduron or Triopac, is advisable at least in cases of suspected perforations.

Oral administration of barium should be avoided as it may change the patient's condition for the worse and thereby complicate operation. It is, moreover, dangerous if aspiration occurs. A further

disadvantage of oral administration as compared with an enema is loss of time. Long radiological procedures may mean that the right moment for operation is missed. It is valueless to endanger the child's life by long drawn out diagnostic procedures, since laparotomy is indicated in any case, at which diagnosis can be completed.

Preliminary Treatment

Apart from local symptoms, intestinal obstruction results in disturbances of the general condition.

Loss of fluid due to vomiting and reduced resorption from the bowel produce dehydration and disturbances in electrolyte balance, such as hypochloraemic alkalosis and hypokalaemia. Intra-intestinal and intraperitoneal transudation produce hypoproteinaemia by loss of plasma. Respiratory difficulties owing to abdominal distension may result in anoxaemia and cyanosis.

Treatment must first of all aim at combating these general disturbances. It would be a grave mistake to expose the baby to the danger of operative shock without adequate preliminary treatment. This consists of the supply of fluid, electrolytes, blood and plasma by intravenous infusion, and employment of a gastro-intestinal suction system. The decrease of abdominal distension by means of a

naso-gastric tube facilitates operative intervention and diminishes operative shock. Intestinal suction is not only of great use in pre-operative treatment, but also during post-operative care, since it prevents paralytic ileus.

Types of Intestinal Obstruction

The most frequent disorders that the surgeon has to keep in mind are summarized in Table 1. It is clear from this Table that as a rule we have to deal with congenital malformations.

TABLE 1
CAUSES OF INTESTINAL OBSTRUCTION IN THE NEWBORN INFANT

Atresia and stenosis: duodenum, jejunum, ileum, colon, rectum, anus
Annular pancreas
Meconium ileus
Disturbances of foetal intestinal rotation: nonrotation, malrotation, common mesentery
Peritoneal bands
Meckel's diverticulum, omphalo-mesenteric duct
Enterogenous cysts (duplication)
Mesenteric cysts
Intestinal polyps
Intussusception
Megacolon (Hirschsprung's disease)
Strangulated inguinal hernia
Strangulated diaphragmatic hernia
Peritonitis

Firstly, the malformation may constitute the immediate cause of the obstruction, as in congenital atresia, annular pancreas, peritoneal bands, etc., or secondly, it may only be a predisposing factor, for instance, in cases of common mesentery, persistent omphalo-mesenteric duct or in diaphragmatic hernia. Thirdly, we have congenital defects, predominantly functional in type, such as meconium ileus and Hirschsprung's disease.

Atresia and Stenosis. In congenital atresia and stenosis of the small intestine, or more rarely of the colon, we have to distinguish between primary and secondary forms.

Primary atresia and stenosis is due to a persistence of epithelial proliferation existing during the fifth to twelfth weeks of foetal life and occluding temporarily the lumen of the intestinal tract. Remaining portions of these epithelial masses may persist as one or several mucosal septa with or without a central opening which obstruct the lumen. Primary atresia and stenosis manifest themselves only by a difference in calibre. No interruption in intestinal continuity can be noticed from the outside (Figs. 4-7).

On the other hand, congenital atresia may also be due to a pathological process during the foetal period which causes secondary obstruction of the

bowel. Pathological processes, such as foetal volvulus, intussusception, incarcerated hernia and meconium ileus, may cause local necrosis of an intestinal segment, thereby producing atresia. These secondary atresias, which are commonly situated at the level of the ileum, are characterized by a gap between the bowel ends or a cord which usually has no mucosal lining. Cicatrization at the ends of the atretic segments and defects in the mesentery are frequent findings. Fibrous nodules on the serous coat and areas containing calcified debris are the remnants of former perforation.

We have observed a case of intestinal atresia in which the collapsed distal stump still contained the remains of an invaginated segment. In another case an incarceration of the lower ileum in an omphalocoele produced a secondary atresia (Figs. 8 and 9).

While in former times operative treatment of atresia or stenosis was rarely successful, modern operative technique and especially adequate post-operative care have considerably improved the prognosis. As a rule the surgeon will try to overcome the obstruction by entero-anastomosis, the method of choice being end-to-end anastomosis as an initial procedure. Enterostomy as a palliative procedure should be considered only in cases in which the obstruction is situated in the terminal ileum or more distal to it. Enterostomy at a higher level is always fatal because of the excessive loss of fluid.

In the performance of entero-anastomosis the difference in size of the pre- and post-stenotic segment may cause some difficulty. In this situation the decompression of the proximal dilated intestine by puncture, suction of direct opening and the injection of normal salt solution into the collapsed narrow distal segment may overcome the discrepancy in size.

In cases of duodeno-jejunoscopy for duodenal stenosis or atresia, the passage of a transanastomotic feeding tube with its top lying in the contracted jejunum is advisable because it allows early feeding and dilatation of the distal contracted loops.

But even in correctly performed anastomosis dilatation of the proximal segment with failure of propulsive activity may persist. Resection of the dilated proximal bulb before end-to-end anastomosis seems therefore to be indicated, especially in cases of secondary atresia with cicatrization of the stumps.

Meconium Ileus. A special kind of intestinal obstruction in the newborn infant occurs in meconium ileus, which requires medical as well as

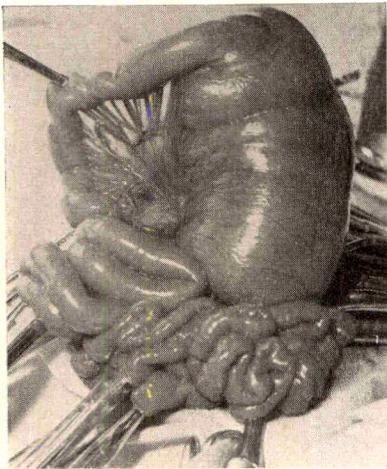


FIG. 4.—Primary stenosis of jejunum.



FIG. 5.—Primary double stenosis of jejunum.

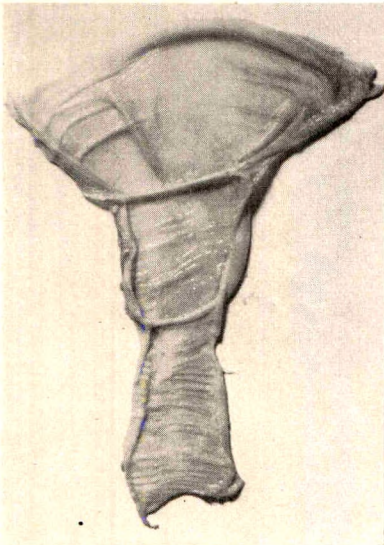


FIG. 6.—Removed and opened specimen (case shown in Fig. 5) with two mucosal folds which formed the stenosis.



FIG. 7.—Small opening in septum causing stenosis (case shown in Fig. 5).

surgical treatment. Meconium ileus is a typical example of intraluminal obstruction, which is caused by an abnormal inspissation of the meconium, especially in the lower segments of the ileum. The abnormal consistency of the meconium is due not only to a deficiency of pancreatic enzymes as a consequence of the co-existing fibrocystic disease of the pancreas; it is rather the expression of a generalized disease of the secreting glands, which is known as mucoviscidosis. The mucous glands of

the bowel, too, produce an exceedingly sticky secretion which is firmly attached to the inspissated meconium.

Operation reveals dilated jejunal loops filled with gas and thick meconium, the ileum appearing like a string of beads due to greyish, putty-like knots. The colon is generally empty (Fig. 10).

The diagnosis is already evident from the radiograph (Fig. 11). The dilated upper loops of the intestine do not present fluid levels in the picture in

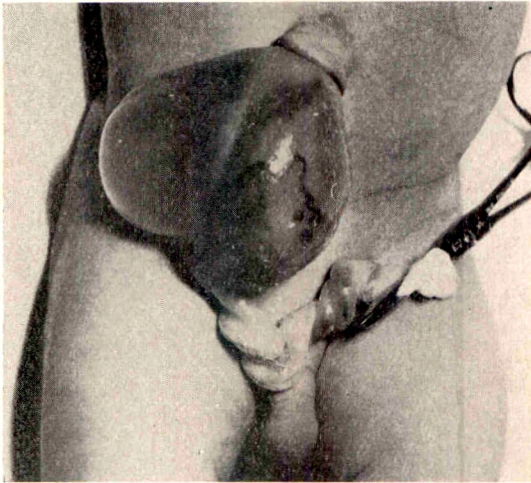


FIG. 8

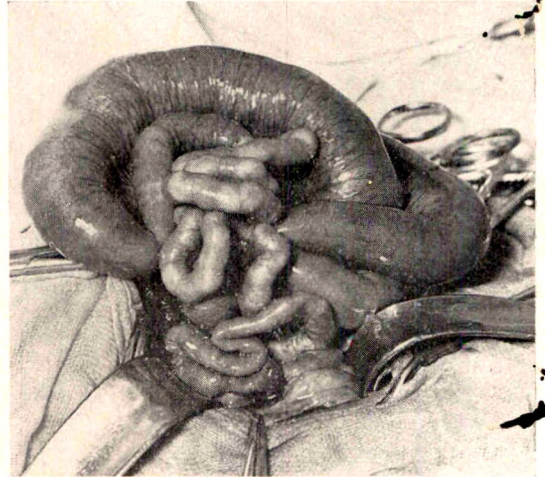


FIG. 10.

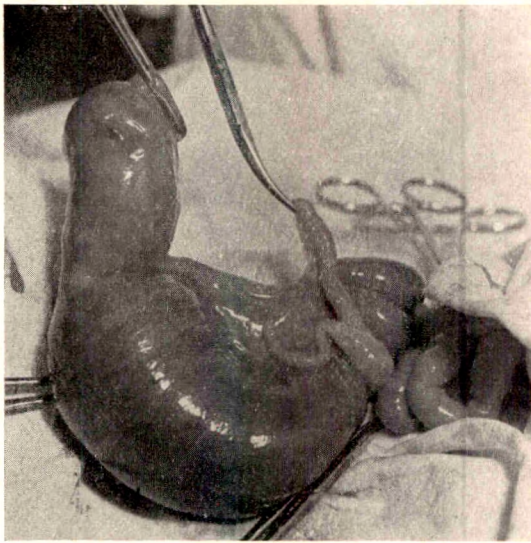


FIG. 9.

FIG. 8.—Omphalocele in a newborn baby with a very narrow umbilical ring and incarcerated transparent mass.

FIG. 9.—Finding at operation in case shown in FIG. 8: secondary atresia of lower ileum owing to strangulation by narrow umbilical ring during foetal period.

FIG. 10.—Typical appearance of meconium ileus.

FIG. 11.—Meconium ileus with several dilated loops of different size without fluid levels. Mottled meconium masses on right side.

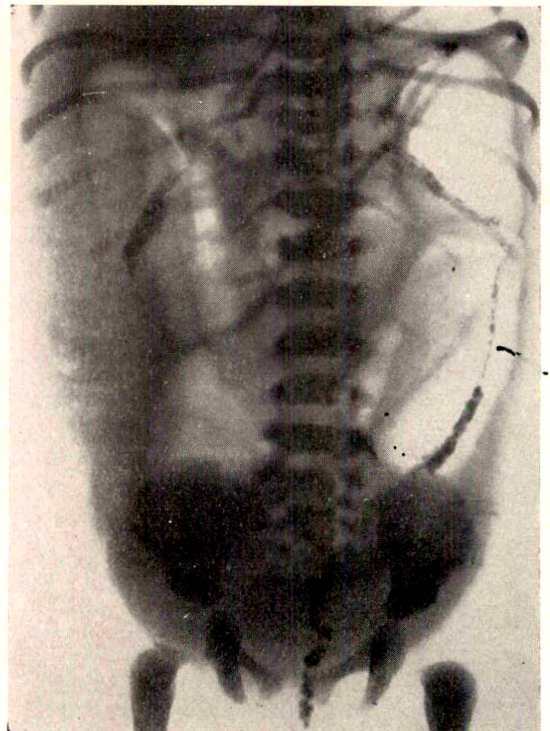


FIG. 11.

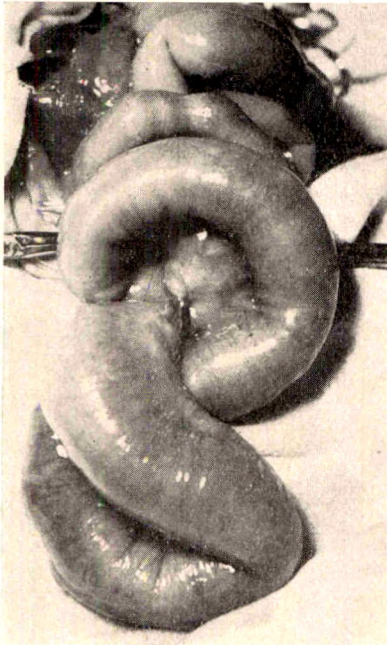


FIG. 12.—Meconium ileus with volvulus.



FIG. 13.—(Case shown in Fig. 12.) Reduction of volvulus reveals a completely squashed loop (secondary atresia).

the upright position because the thick gluey meconium adheres to the intestinal wall. The meconium masses manifest themselves by granular spots. The mottled appearance is due to infiltration of the meconium by small air bubbles.

An enema with a contrast medium shows the colon, which is free of meconium and has the appearance of a so-called 'microcolon'.

Meconium ileus may produce several complications even during the foetal period. The accumulated meconium masses may cause ischaemia, necrosis and perforation of the intestinal wall, thus producing aseptic meconium peritonitis, which may cause adhesions and strangulations. These cases present typical calcified granulations in the peritoneal cavity corresponding to foreign body reactions.

Not infrequently the enlarged and heavy loops of the upper intestine become twisted upon themselves and give rise to volvulus formation with or without secondary atresia of the strangulated segments. Fig. 12 represents a volvulus of this origin. Reduction of the volvulus reveals a completely squashed loop (Fig. 13). In this way secondary atresias are formed. In the case of Fig. 14 the same process took place at an early stage of foetal life. The result is a complete interruption of the continuity of the bowel.

In the treatment of meconium ileus the following facts are of crucial importance. We know that it is impossible to estimate the degree of severity by clinical and radiological investigations, or to distinguish uncomplicated from complicated cases with volvulus, perforations and secondary atresias. Laparotomy is therefore indicated in any case.

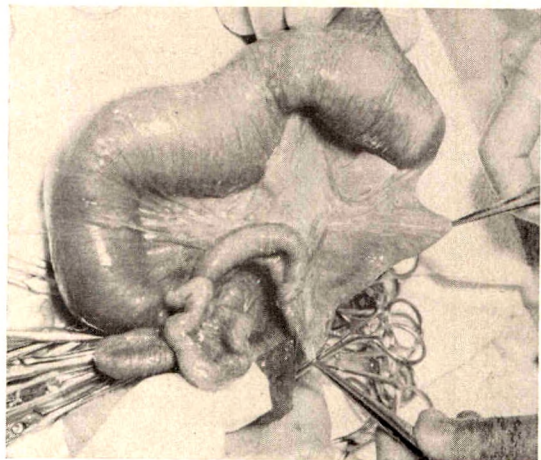


FIG. 14.—Meconium ileus with secondary atresia of lower ileum caused by volvulus at an early foetal stage.

In uncomplicated cases the first thing is to relieve the increasing and dangerous intestinal distension by suction. The removal of the obstacle, the sticky thick meconium masses in the ileum, cannot possibly be performed by mechanical procedures. On the other hand, it has been proved that after administration of pancreatic enzymes the meconium may be expelled spontaneously in a few days. Therefore we make a small incision in the lowest portion of the distended intestine, deflate the upper loops and introduce a powdered preparation of pancreatic enzymes into the intestinal lumen. Before we close the abdominal wound a tube is passed through the nose into the stomach and duodenum under direct vision. In this way the intestine can be deflated during subsequent days and further proteolytic enzymes can be instilled through the tube.

While this simple treatment is successful in uncomplicated cases, more severe forms require enterostomy, through which enzyme instillations can be administered. Although results as regards relief of the obstruction seem at first glance to be satisfactory, long-term results are disappointing. Most of these babies die sooner or later of overwhelming pulmonary infection in spite of adequate diet, administration of pancreatic enzymes and antibiotic treatment.

Abnormal Bowel Positions. Other not infrequent conditions causing intestinal obstruction in the newborn infant are abnormal positions of the bowel

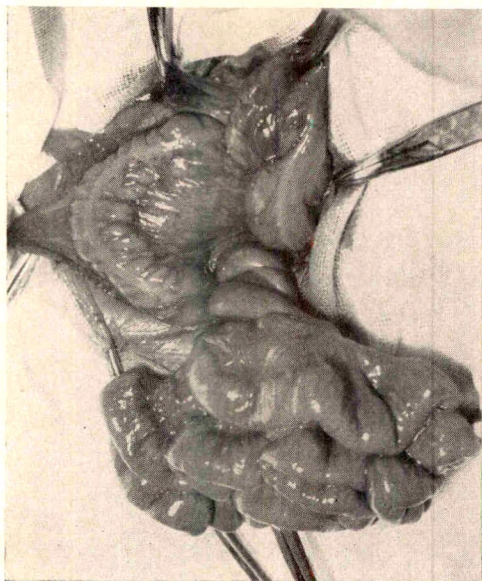


FIG. 15.—Volvulus in a newborn infant with common mesentery.

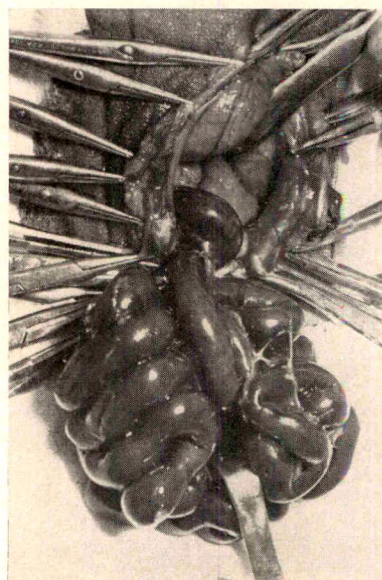


FIG. 16.—Infarction of intestine in a newborn infant owing to common mesentery with volvulus.

due to lack of normal rotation of the midgut during the foetal period. The recognition of such conditions often demands considerable spatial imagination on the part of the surgeon.

The normal position of the bowel is reached by a rotation of the midgut of 270° in an anti-clockwise direction. The midgut represents that portion of the alimentary tract from the duodenum to the middle of the transverse colon, which is supplied by the superior mesenteric artery. To reach a normal position, the mesentery of the ascending colon has to become fixed to the right posterior abdominal wall.

The rotation may be incomplete, it may stop after 90° or 180° or take place in a reverse direction. In addition, failure of attachment of the mesentery along the right lateral and posterior abdominal wall is nearly always present, but this anomaly, so-called common mesentery, may also be encountered in cases with normal rotation.

The common mesentery can obviously give rise to twisting of the entire mass of the small intestine and colon around the small mesenteric root, which generally takes place in a clockwise direction (Fig. 15). The twisted mesenteric pedicle may strangulate the inferior part of the duodenum and produce symptoms of duodenal stenosis. In rare cases, in which the twisted mesenteric root strangulates the mesenteric vessels, infarction of the entire intestinal mass may ensue (Fig. 16).

Another anomaly causing obstruction of the duodenum results from compression of the lower duodenum by an overlying caecum or ascending colon. This condition may be encountered in cases with incomplete or reversed rotation, in which the caecum is placed in the duodenal area and becomes fused with the posterior abdominal wall.

A third form of obstruction may be seen in cases with reversed rotation when the duodenum reaches its final position in front of, and the transverse colon behind, the mesenteric root. This condition, known as retroposition of the transverse colon, may produce an obstruction of the proximal colon, especially if it is complicated by an additional volvulus. Visualization of the colon by radiography with contrasting barium almost always supplies significant information. When the caecum and ascending colon are displaced to the left and upper part of the abdomen a volvulus of the midgut should always be suspected (Figs. 17 and 18).

Even so-called internal hernia, or mesocolic hernia, may be due partly to anomalous intestinal rotation. The tendency of the proximal colon to reach its normal position on the right, independently of previous foetal rotation, may in cases of non-

rotation or reversed rotation lead to partial or total envelopment of the small intestine by the ascending mesocolon. Thus internal hernia is produced in which intestinal loops may be incarcerated (Fig. 19).

Operative treatment of the abnormal position and rotation should not only comprise the reduction of a volvulus or the severance of strangulating bands, but the ascending colon should be fixed to the right posterior abdominal wall in a normal position. Our own experience with mesenteric vessels has taught us that fixation at the right site is absolutely essential in order to obtain optimal blood supply.

Enterogenous Cyst. Another congenital malformation which has to be taken into account in cases of intestinal obstruction is the enterogenous cyst, or duplication of the bowel, which is seen in about 20% of cases even in the neonatal period.

These structures, which may be tubular, cystic or diverticular, can branch out from the entire bowel, but they usually lie in the region of the lower ileum and caecum. In spite of this, they have embryologically nothing to do with Meckel's diverticulum. The duplications are due to disturbances during an early foetal period in which



FIG. 17.—Retroposition of transverse colon (reversed rotation) with additional volvulus. Caecum lies in an anomalous position in left upper side of abdomen. Filling defect of transverse colon due to compression by twisted mesenteric pedicle.



FIG. 18.—Diagram of case shown in Fig. 17.



FIG. 19.

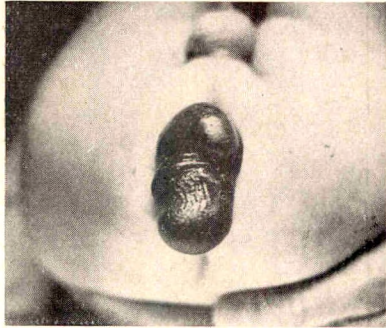


FIG. 20.

FIG. 19.—Internal hernia containing several incarcerated loops. Hernial sac is formed by mesentery of ascending colon.

FIG. 20.—Intussusception in a newborn baby with intussusceptum protruding from anus owing to ileal duplication.

FIG. 21.—Resected ileo-caecal specimen from case shown in Fig. 20. Note enterogenous cyst in lower ileum.

FIG. 22.—Multilocular lymphatic mesenteric cyst producing intestinal obstruction and stasis of adjacent bowel segment.

FIG. 23.—Hour-glass-shaped chylous mesenteric cyst which contained large quantity of yellow, milky fluid.

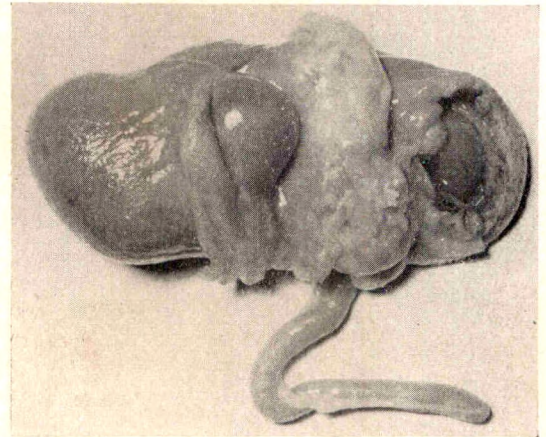


FIG. 21.

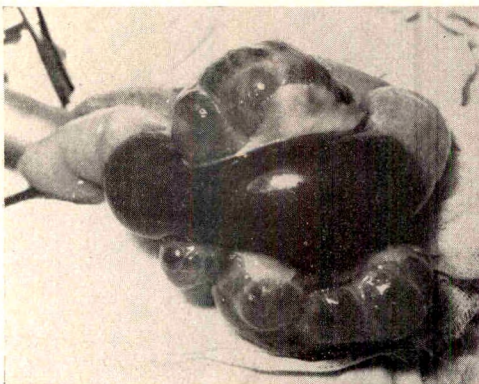


FIG. 22.

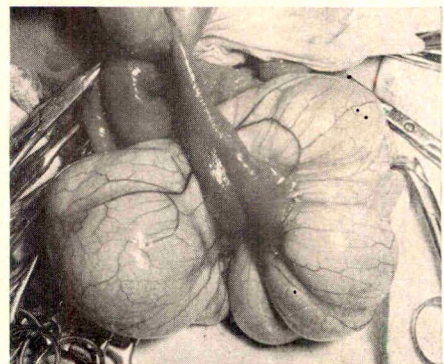


FIG. 23.

The chorda dorsalis is separated from the entoderm. These cystic structures, closely attached to some portion of the alimentary tube, grow continuously in size by retention of secreted mucosal fluid, thereby causing obstruction of the intestinal lumen.

Since these duplications are supplied with blood by the same vessels as is the adjacent bowel, it is impossible to resect the cyst without impairment of the blood supply to the contiguous intestinal segment. Therefore the segment in question has also to be resected.

Cysts of this type may not only produce intestinal obstruction, but they may also act as a leading point in the development of intussusception. Fig. 20 shows a newborn baby with intussusception, the tip of the intussusceptum protruding from the anus. It contained a single cystic tumour. Surgical reduction of the intussusception presented no difficulty. After reduction, the cystic tumour proved to be a duplication of the lower ileum which had passed the whole colon within a few hours. Ileo-caecal resection was performed (Fig. 21) and the post-operative course was uneventful.

Mesenteric Cyst. Other structures, which have to be differentiated from enterogenous cysts, are lymphatic mesenteric cysts. These tumours rarely cause intestinal obstruction in the newborn infant. The cysts are thin-walled and multilocular and often have the shape of an hour-glass. They contain serous, colourless or chylous yellowish fluid (Figs. 22 and 23). Smaller cysts can be dissected out from the mesentery, while large ones require intestinal resection and end-to-end anastomosis.

Hirschsprung's Disease. Lastly I should like to make brief mention of Hirschsprung's disease or aganglionic megacolon.

Newborn babies with this disease almost always show difficulty in evacuation of meconium, constipation, vomiting and abdominal distension, all symptoms of intestinal obstruction which, however, vary in intensity.

Often an obstruction of the small bowel is suspected, particularly as plain radiography shows dilated loops with fluid levels. To exclude this a contrast enema is absolutely essential. It shows that the dilatation is situated in the colon. The picture typical for Hirschsprung's disease with contracted rectosigmoid is, however, frequently not so marked in the newborn baby as it is some weeks later. In case of doubt a biopsy from the rectal musculature should be performed. Microscopical examination will prove whether ganglion cells are present or not.

One rare though severe complication of Hirschsprung's disease, which may occur in the first days of life, is perforation of the distended colon (Fig. 24). We have observed it in three cases: twice in the region of the left colonic flexure and once in the caecum. In all three cases colostomy was performed at the site of perforation with good results.

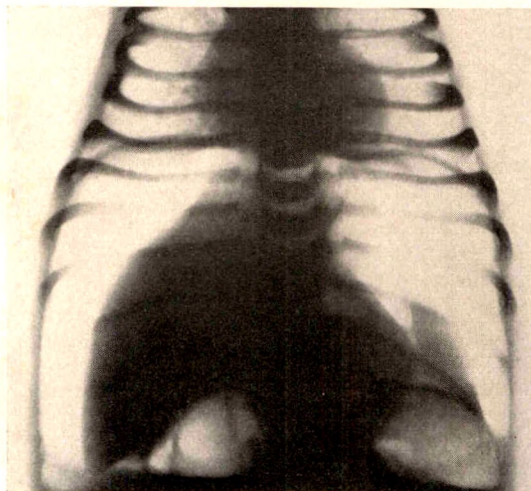


FIG. 24.—Pneumoperitoneum after perforation of colon in a 2-day-old baby suffering from Hirschsprung's disease.

In the treatment of megacolon in the newborn baby conservative measures will, as a rule, be resorted to at the start with frequent enemas to combat the gaseous distension. In most cases this will prove successful for some time. Should difficulties arise in controlling the distension, temporary colostomy is advisable. Nevertheless, we do not hesitate in such cases to perform rectosigmoidectomy by Duhamel's method even in the first few months of life. This retrorectal pull-through is technically simple, as the rectum has to be mobilized only on its dorsal side, which is easy to accomplish. The intervention is therefore relatively short and produces no shock. It prevents secondary strictures at the site of the anastomosis and disturbances of bladder function.

We have employed this method in 15 cases, six of whom were infants aged from 6 weeks to 8 months. Results were very satisfactory regarding healing of the megacolon, but later investigation of these children showed that they suffered from numerous evacuations, some even from actual diarrhoea, as a result of the destruction of the internal sphincter.

We therefore advise the following modification of Duhamel's procedure: we incise the posterior wall of the rectum 1.5 cm. above the internal sphincter, thus conserving this important muscle. The proximal stump of the colon is pulled through this incision and not through one at the level of the anus. Details of this special technique will be published shortly. The apparent level of the transitional zone in young infants may be misleading; biopsy of the colon muscle tissue during operation is therefore advisable.

A difficult problem in the newborn period, which, however, arises only seldom, is presented by those cases in which the aganglionic zone extends throughout the whole colon as far as the lower ileum. Deflation by an enema is in these cases ineffective and the clinical picture corresponds to that of a lower stenosis of the small bowel. We recently observed such a case, which at operation showed a greatly dilated and hypertrophic lower ileum (Fig. 25). Ileostomy was performed and total colectomy was provided for at a later date. Unfortunately the infant died of peritonitis. Microscopical examination revealed that the hypertrophic ileal loops contained ganglion cells in normal numbers whereas the terminal part of the ileum contained only a few ganglion cells, and throughout the caecum and colon they were completely absent. The peculiar thing about this case was that the child showed no symptoms of intestinal obstruction as long as she was breast-fed. Only after changing to artificial feeding did such symptoms appear.

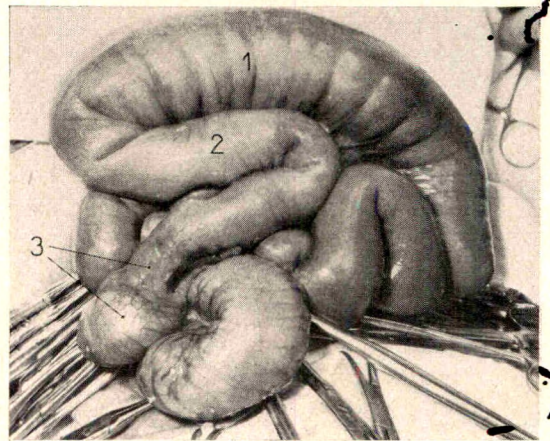


FIG. 25.—Hirschsprung's disease with aganglionic zone throughout colon and terminal ileum: 1 = hypertrophic and dilated ileum with normal number of ganglion cells; 2 = only few ganglion cells; 3 = ganglion cells completely absent.

In conclusion I should like to emphasize that I am fully aware of the incompleteness of my remarks concerning intestinal obstruction in the newborn baby. Many problems could only be touched upon.

Intestinal obstruction in a newborn baby is always a delicate and critical matter demanding rapid decisions. Success in these cases depends not only on early diagnosis and appropriate operation, but also upon the quality of pre- and post-operative care, of suitable anaesthesia, and, last but not least, upon the constant and untiring efforts of our nurses.

SIMULTANEOUS INTRA- AND EXTRAPULMONARY SEQUESTRATION*

BY

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Pulmonary sequestration has attracted considerable attention in recent years. Many papers reporting typical cases have appeared in the literature. Repetition of material already extensively reported will not be attempted (Bariéty and Coury, 1947; Pryce, Sellors and Blair, 1947; Bruwer, Clagett and McDonald, 1950, 1954; Kergin, 1952; Santy, Bérard, Gaby and Huu (1952); Boyd, 1953; Hertzog, Toty, Personne and Gilbert, 1953; Razemon, Houcke and Razemon, 1953; Monod, 1954; Boyden, 1955, 1958; Bruwer, 1955; Pryce, 1946; Smith, 1956; Procházka and Steinhart, 1957).

The case described here is a very rare form of pulmonary sequestration, which justifies its publication.

Case Report

The patient was a 15-month-old boy (No. 1323/58) who at the age of 3 weeks developed pneumonia, seen in the radiograph as a pericardial infiltration above the diaphragm (Fig. 1). Despite the usual antibiotic therapy, it subsided surprisingly slowly (Fig. 2). A follow-up radiograph at 11 months of age showed a sharply defined elliptical shadow, the size of an egg, lying paravertebrally below the diaphragm and superimposed on the gastric bubble (Figs. 3 and 4). Following radiological examination, including upper gastro-intestinal barium studies, retroperitoneal air insufflation, bronchography and pyelography, the provisional diagnosis of retroperitoneal tumour, probably of neurogenic origin, was made. Surgery was advised after further regression of the pneumonitis.

The operation (Kafka, Brodský, Kudrnová, anaesth. Drapka) was performed on October 18, 1958. An oblique incision was made in the left epigastrium. The tumour was found to be on the posterior surface of the stomach (Fig. 5) on the fundus and on the cardia. It was a thin-walled cyst fixed flat against the stomach and was separated by sharp dissection. Its superior end continued as a narrower cylindrical cyst, lying on the oesophagus, right up through the hiatus. The lumen of this narrow cyst was separated from its gastric portion only by an internal membrane.

The oesophagus was pulled downwards and the cyst further dissected. On opening the cyst wall and inserting a probe, it was found that the cyst continued into the thorax in a dorso-latero-cranial direction. By prolonging the incision through the seventh intercostal space an additional thoracophrenotomy was performed. The cyst, or rather its stem, 10 × 12 mm. in diameter, diverged from the oesophagus to enter the dorso-basal segment of the left lower lobe. A large coiled artery ran into it, traversing the diaphragm and arising from the abdominal aorta. This was ligated and a resection of the dorsobasal segment, together with the entire cystic structure, was carried out (Fig. 6).

Specimen (Fig. 7). The resected specimen consisted of two parts. The superior portion was in the shape of a triangle, at the apex of which were bronchi, artery and vein running into the resected segment of the left lower lobe. On probing, the bronchus did not communicate with the cyst, which formed the posterior wall of the resected segment. The upper portion of the cyst was thick-walled, containing almost cartilaginous elements; its distal part narrowed into a thick stalk 6-7 cm. long, without interruption of the cyst lumen. An ovoid, thin-walled segment the size of an egg was situated on the inferior end.

Histology. (Žaková, Second Institute of Pathological Anatomy, Charles' University, Prague; Case No. 3164/58.) The wall was formed by two layers of smooth muscle fibres. Exterior to this was a layer of connective tissue showing elastic degeneration, and scattered seromucous gland. Ciliated cylindrical epithelium on a basal membrane formed the cyst lining (Figs. 8 and 9).

The post-operative course was uneventful; one year after operation the patient's condition now appears excellent.

Discussion

In the present communication we wish to outline certain characteristics of this syndrome: the simultaneous occurrence of intra- and extralobar sequestration, the subdiaphragmatic position of a part of the dumb-bell-shaped cyst, the blood supply and, finally, problems of diagnosis before and during operation.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

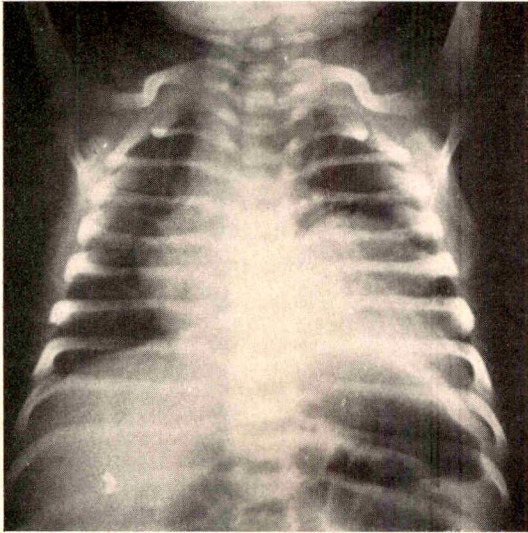


FIG. 1.—Admission radiograph showing consolidation of left lower pulmonary field.

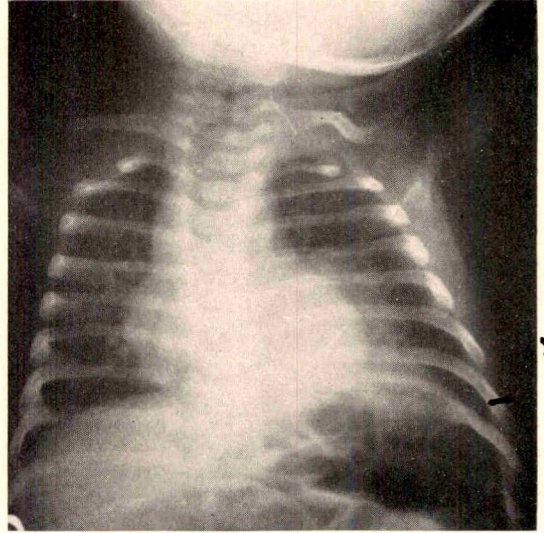


FIG. 2.—Radiograph taken two months after that of Fig. 1, showing slow improvement of pulmonary condition following chemotherapy.

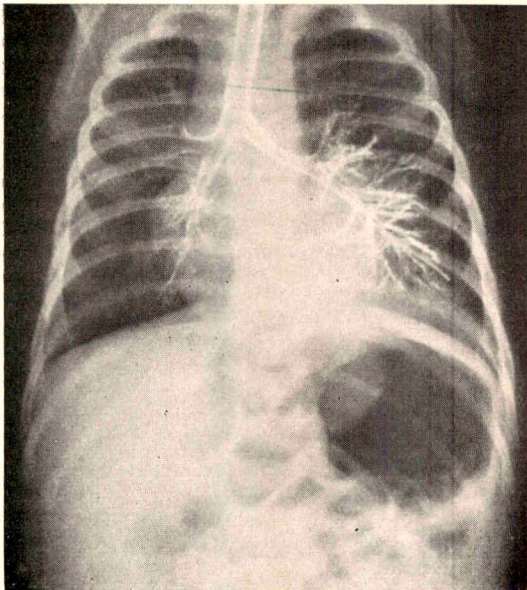


FIG. 3.—Bronchogram showing shadow below diaphragm superimposed on gastric bubble.

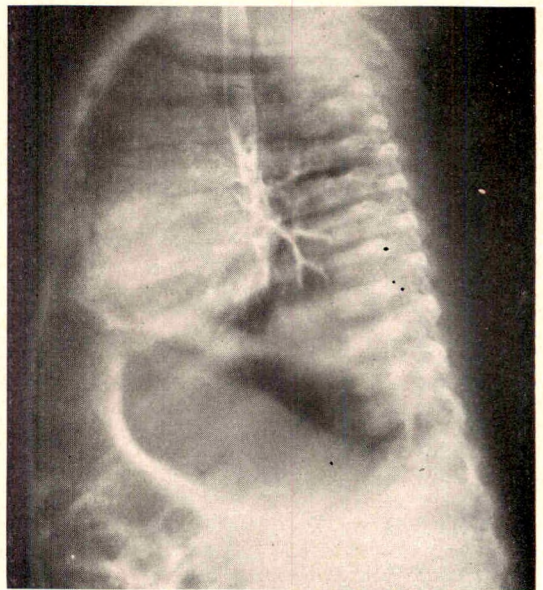


FIG. 4.—Bronchogram: lateral view showing shadow below diaphragm just in front of vertebral column.

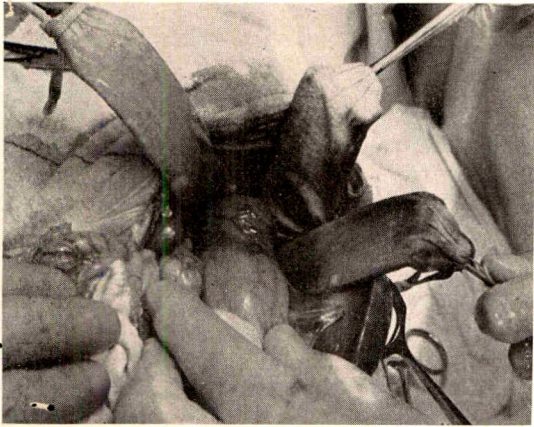


FIG. 5.—At operation the tumour was found lying at posterior surface of stomach.

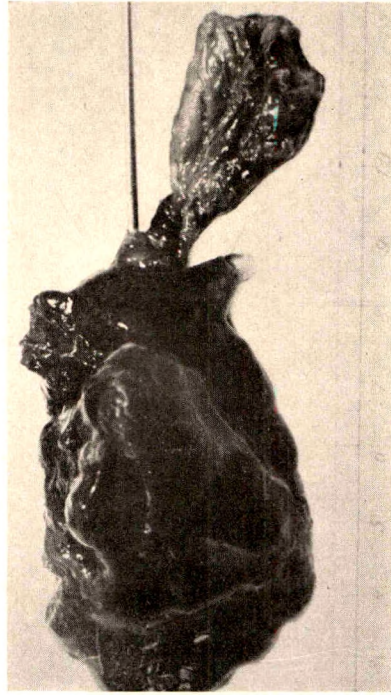


FIG. 7.—Excised specimen.



FIG. 9.—Section of cyst wall (high magnification).

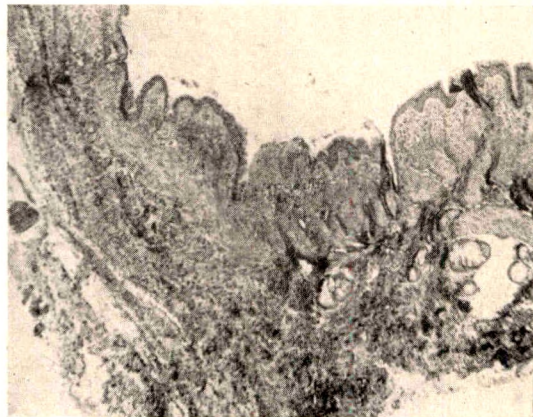


FIG. 8.—Section of cyst wall.

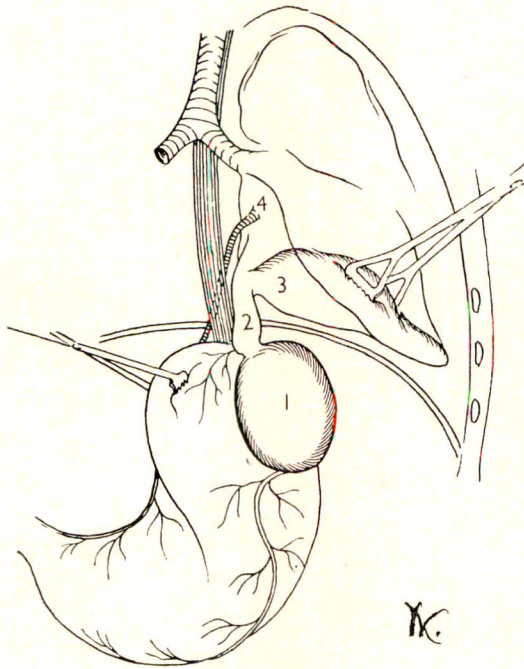


FIG. 6.—Schematic drawing showing findings at operation: 1. Spherical cyst; 2. Tubular prolongation; 3. Left lower pulmonary lobe; 4. Bronchial artery.

Neither aetiology nor classification of this disease entity have been agreed upon (Gebauer and Mason, 1959), and the term sequestration itself does not seem to cover the case. Since this term has been widely applied as a result of publications by Pryce *et al.* (1947) and others, we shall continue to use their terminology. The term "foregut cyst" (Hössli, 1950; Roemer and Mollowitz, 1957) or 'dysembryopathy' (Bert and Fischer, 1910; Petříková, Polák and Stolz, 1952; Breton and Dubois, 1957) seems more accurate.

It is known that pulmonary sequestration is one of a group of developmental defects occurring at the site of differentiation of the gastro-intestinal and respiratory tracts from the foregut. It naturally follows that various structures in the lower thoracic area may be involved (Cole, Alley and Jones, 1951), particularly the lower lobe arteries (Cole *et al.*, 1951; Findlay and Maier, 1951; Fry, Arnold and Miller, 1953), mediastinum (Maier, 1948), pericardium (Ladd, 1936; Rusby and Sellors, 1945; Warner, Britt and Riley, 1958) and diaphragm (Cockayne and Gladstone, 1917; Raymond *et al.*, 1956).

The majority of cases present a relatively simple lobar form of pulmonary sequestration (Boyd, 1953; Bruwer *et al.*, 1954; Bruwer, 1955), often supplied by an atypical systemic artery, also referred to as a

bronchogenic cyst (Fry *et al.*, 1953; Gross, 1953), Flimmerepithelcysts (Zadek and Riegel, 1958), congenital lung cyst (Kergin, 1952), etc.

Extralobar sequestration has a more complex character. We find it termed 'lower accessory lung' (DeBakey, Arey and Brunazzi, 1950), pulmonary aberrations, supranumerary lung (Gans and Potts, 1950; Raymond, Hardy and Robbins, 1956; Boyden, 1958) located in the pleural cavity (Rusby and Sellors, 1945) as well as in the mediastinum (Maier, 1948) or elsewhere. Some authors do not make a genetic differentiation and maintain that these are quantitative variations of the same developmental defect (Bert and Fischer, 1910; Borovanský and Hněvkovský, 1929; Breton and Dubois, 1957).

The site of the lesion and its embryonic stage determine the degree of tissue differentiation and the location and nature of the malformation. Maier (1948) maintains, for example, that there is no formal differentiation between bronchogenic and enterogenic cysts.

Since the aetiology and exact origin of such developmental errors are still not clear, we do not feel qualified to comment upon them.

Only rarely do both extra- and intralobar sequestration occur simultaneously. And even more rarely is this combined with ectopic location of the extralobar part in the abdominal cavity or below the diaphragm. Cases of isolated ectopy are mentioned by Valle and White (1947) and Raymond *et al.* (1956). Very complex malformations may occur. Such a condition was found in our patient, where a cyst of the stomach and oesophagus was connected with a pulmonary cyst supplied by an anomalous artery arising from the abdominal aorta.

Mention must be made here of what Gross (1953) calls 'duplications of the alimentary tract'. Two cases were presented with simultaneous occurrence of enterogenic cysts in thoracic and abdominal cavities. These should be considered in the differential diagnosis of extrapulmonary sequestration.

From the surgical point of view it is interesting that pulmonary sequestration with arterial anomalies was a problem some 10 years ago, as shown by reports of operative deaths or severe complications in relation (or without relation) to surgery. Fatal haemorrhage was reported by Harris and Lewis (1940), Butler (1947) and Douglass (1948)—see Fry *et al.* (1953). The extensive work of Pryce *et al.* (1947) and others acquainted thoracic surgeons with the problem involved, and today the literature contains more than 110 cases; over 100 have been reported by Bruwer (1955) and 11 cases from the Czecho-Slovakian literature may be added. This

does not include reports of simple bronchogenic cysts (without anomalous artery) with an intrapulmonary or mediastinal localization.

In most uncomplicated cases pre-operative diagnosis is not difficult. Repeated lung infection and a shadow on the radiograph in the region of the dorsobasal pulmonary segment pointing caudally to the midline indicate the lines along which further investigation should be carried out (Wyman and Eyer, quoted by Bruwer (1955)).

There are, of course, circumstances which complicate the diagnosis. These are in the first place inflammatory processes, including lung abscess and tuberculosis, or non-inflammatory processes, such as atelectasis, bronchiectasis, etc. In the second place, difficulties may be encountered in differentiation from pulmonary or extrapulmonary neoplasms

(Barthel, 1958). Cases of pulmonary sequestration treated as tuberculosis, even including thoracoplasty, or as pneumothorax from a burst lung abscess have been reported (Table 1).

Even in the course of operation to make the correct diagnosis is not always simple or even possible. Fry *et al.* (1953) admit having performed an operation, supposedly for an enterogenic cyst, without being directed to the right conclusion even by the discovery of an extension through the diaphragm. Only histological examination revealed that it was a case of a pulmonary sequestration.

Similarly, in our case pulmonary sequestration was not suspected, in spite of the finding of a gastric cyst, until probing of the oesophageal cyst revealed its true extent.

TABLE 1
PULMONARY SEQUESTRATION TREATED SURGICALLY IN CHILDREN UNDER 20 YEARS

Author	Cases (no.)	Sex	Age (yr.)	Site	Clinical Diagnosis	Anomalous Artery Derived from:	Operation
Rusby and Sellors (1945)	1	F	19	Left extralobar	Pulmonary cyst or tumour of mediastinum	Pulmonary or bronchial artery	Extirpation
Ravitch and Hardy (1949)	2	M M	12½ 6	L.L.L. R.L.L.	Infected cyst " "	Thoracic aorta (3) Intercostal artery	Lobectomy Lobectomy
Gans and Potts (1950)	1	F	5/12	Left extralobar communication to oesophagus	Oesophageal diverticulum	Pulmonary artery	Extirpation
Hössli (1950)	1	M	5	L.L.L. communication to stomach	Pulmonary abscess		Lobectomy
DeBakey <i>et al.</i> (1950)	1	F	7	L.L.L.	Pulmonary cyst (dermoid)	Thoracic aorta	
Cole <i>et al.</i> (1951)	1	M	3	L.L.L.	Cyst	Thoracic aorta	Lobectomy
Kergin (1952)	3	M F F	17 19 16	L.L.L. L.L.L. R.L.L. Intra- and extralobar	Cystic disease Infected cyst Intralobar sequestration	Thoracic aorta Subdiaphragm Intercostal artery	Lobectomy Lobectomy Lobectomy
Boyd (1953)	6	M M F F F M	7 5 4 13 9½ 6	R.L.L. R.L.L. L.L.L. L.L.L. L.L.L. L.L.L.	Tuberculosis Pulmonary affection " " " " " " " "	Intercostal artery Subdiaphragm Thoracic aorta " " Subdiaphragm "	
Fry <i>et al.</i> (1953)	1	M	19	R.L.L.	Pulmonary cyst (abscess)	Subdiaphragm	Lobectomy
Čermák, Váňa and Rozhold (1955)	2	F F	6 14	R.L.L. R.L.L.	Bronchiectasis ?	Subdiaphragm Thoracic aorta (3)	Lobectomy Lobectomy
Smith (1956)	1	M	18	L.L.L.	Bronchiectasis	Thoracic aorta	Lobectomy
Procházka and Steinhart (1957)	4	M M M F	6 5 6 7	L.L.L. L.L.L. R.L.L. L.L.L.	Tumour or pulmonary cyst Vulvular pneumothorax Sequestration Cyst (Tb empyema)	Thoracic aorta " " Subdiaphragm Thoracic aorta	Segmental resection Lobectomy Lobectomy Thoracoplasty else- Lobectomy [where]
Warner <i>et al.</i> (1958)	2	F M	3 7½	Intrapulmonary Extrapulmonary (pericardial defect)	Cyst Mediastinal cyst	Subdiaphragm (4) Pulmonary and bronchial artery	Lobectomy Extirpation
Kafka and Beco	1	M	1¼	L.L.L. and extralobar (sub-diaphragm)	Neurogenic tumour	Subdiaphragm	Segmental resection and extirpation (thoracophrenolaparotomy)

Conclusions

The history of our case clearly shows signs typical of pulmonary sequestration, which together with the type of infiltration shown by radiography in the left lower lobe should have directed us towards a correct diagnosis.

The misleading element was the finding of an abdominal tumour in a paravertebral position. This and its shape appeared to indicate a ganglioneuroma.

Tomography and retroperitoneal insufflation were not helpful, since the tumour was in fact partly situated in the retroperitoneal space.

Barium meal showed no pathological changes. On bronchography three branches of the dorsobasal bronchus did not fill right up to their periphery, which was considered incidental to the suspected postpneumonic condition.

For these reasons operation was started with a diagnosis of retroperitoneal tumour, a neurinoma, and no connexion was at first seen between the two conditions, pulmonary and abdominal.

In the course of operation we were surprised to find that (1) the mass was not a ganglioneuroma, (2) it was not wholly retroperitoneal, arching into the abdominal cavity and connecting with the stomach, and (3) it had penetrated through the hiatus along the oesophagus into the thoracic cavity.

Only probing the cyst lumen revealed that the cyst continued high up into the thorax, and the approach was widened into a thoraco-phrenolaparotomy. It then became clear that this was a case of pulmonary sequestration. The anomalous artery could be severed and the entire cystic mass was removed.

Summary

A rare case of dysembryoplasia (foregut cyst) in the region of the respiratory and upper alimentary tracts is described, falling under the heading of pulmonary sequestration as known in the literature.

Thoracophrenolaparotomy in a boy of 15 months revealed connecting masses of cysts, localized in the left inferior lobe (intralobar sequestration with an aberrant artery), passing to the oesophagus (extralobar pulmonary sequestration) and through the hiatus to the stomach (forming the subdiaphragmatic part of the tumour).

The entire cystic complex was removed.

Diagnostic errors and special anatomical conditions in the described case are pointed out. The discussion is supported by a Table covering exclusively surgical cases in children.

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PULMONARY SEQUESTRATION*

BY

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Pulmonary sequestration is a developmental anomaly of the pulmonary and cardiovascular system. It consists of dissociated, non-functioning lung tissue which is supplied by aberrant arteries and has no communication with the normal bronchial system. It may be divided into two types, intralobar and extralobar. This anomaly has become an important and interesting clinical problem in the past 10 years. Most of the cases were diagnosed and treated as lung abscess, empyema or bronchiectasis because the real diagnosis had been overlooked.

The number of reported cases has increased rapidly during the last 10 years. Nevertheless in 1958 Eaker, Hannon and French discovered only 104 cases; Warner, Britt and Riley (1958) reported three cases. In addition I would like to report three cases from the Bremen Children's Hospital.

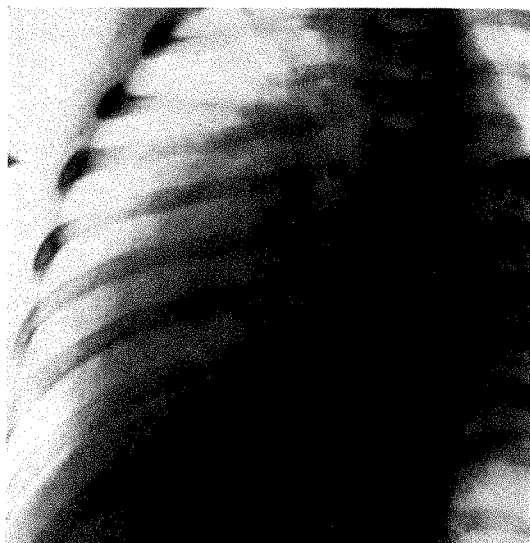


FIG. 2.—Case 1. On rotation shadow is seen to lie in posterior region of thorax. An area of calcified density is visualized.

Case Reports

Case 1. A 6-month-old girl was admitted because of high fever. A radiograph (Fig. 1) showed an area of opacity in the right lung field. On rotation of the patient it was seen to be in the lower posterior region of the chest wall, and an area of calcified density was visualized (Fig. 2). The heart and mediastinum were shifted to the left side. At operation there was a mass about the size of two fists arising from the right lower lobe, which could not be detached from the lung or diaphragm. Therefore the lower lobe was resected. As we tried to free the adhesion from the diaphragm an accessory artery the size of a pencil was seen arising from the thoracic aorta and running to the lower lobe. Moreover there was an opening about 2.5 cm. in diameter on the right side of the diaphragm containing a mushroom-shaped protrusion of liver, which communicated with the lower lobe through the adhesion tissue.

Unfortunately the child died immediately after the operation. The macroscopical specimen showed a small cystic formation of the whole lower lobe, part of which became a solid yellow area. There was normal lung tissue only at the anterior margin of the lobe. At the

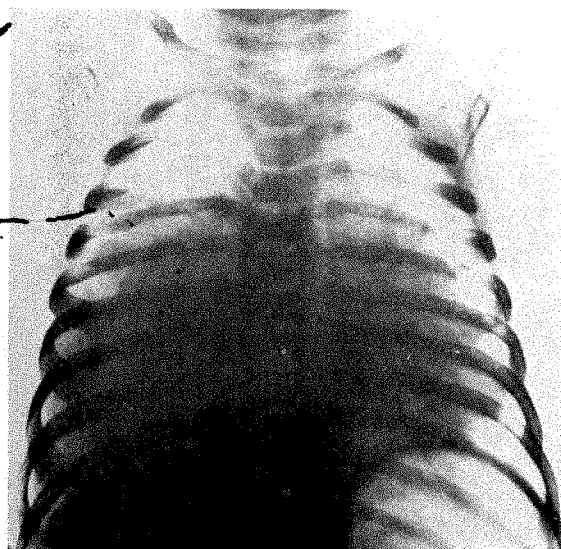


FIG. 1.—Case 1. Large opacity in right hemithorax with displacement of heart and mediastinum to left side.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

base of the lung there was a communication of the arterial branch into the liver through the opening in the diaphragm. Histological examination showed that the cysts were lined with bronchial epithelium (some ciliated) containing cellular debris and desquamated epithelium.

According to the reported cases in the literature, this case is a rare one. Besides a right intralobar pulmonary sequestration there was a defect of the diaphragm and communication between the sequestration and the liver.

Case 2. A 14-year-old boy without symptoms was admitted because of a tumour shadow in the lower part of the right thorax, which had been found accidentally two years previously on serial radiological examination. There was a dense oval shadow in the posterior part of

the right lower lobe (Fig. 3a, b), which revealed a fluid level on the cranial side and had two round protrusions. Bronchographic examination (Fig. 3c) showed that the bronchus segment no. 6 was displaced upward, and no. 9 and no. 10 forward. At operation the lower lobe was seen to be composed of many small cystic tumours. It was impossible to dissect these masses from the lower lobe and therefore lobectomy was performed. The pulmonary ligament contained an abnormal artery about the size of a pencil from the aorta to the lower lobe. There was no post-operative complication and the radiograph showed a satisfactory result (Fig. 3d).

Histological examination showed an area of extensive widening of the bronchi with two large cystic formations in the lower lobe. They were irregularly lined with simple

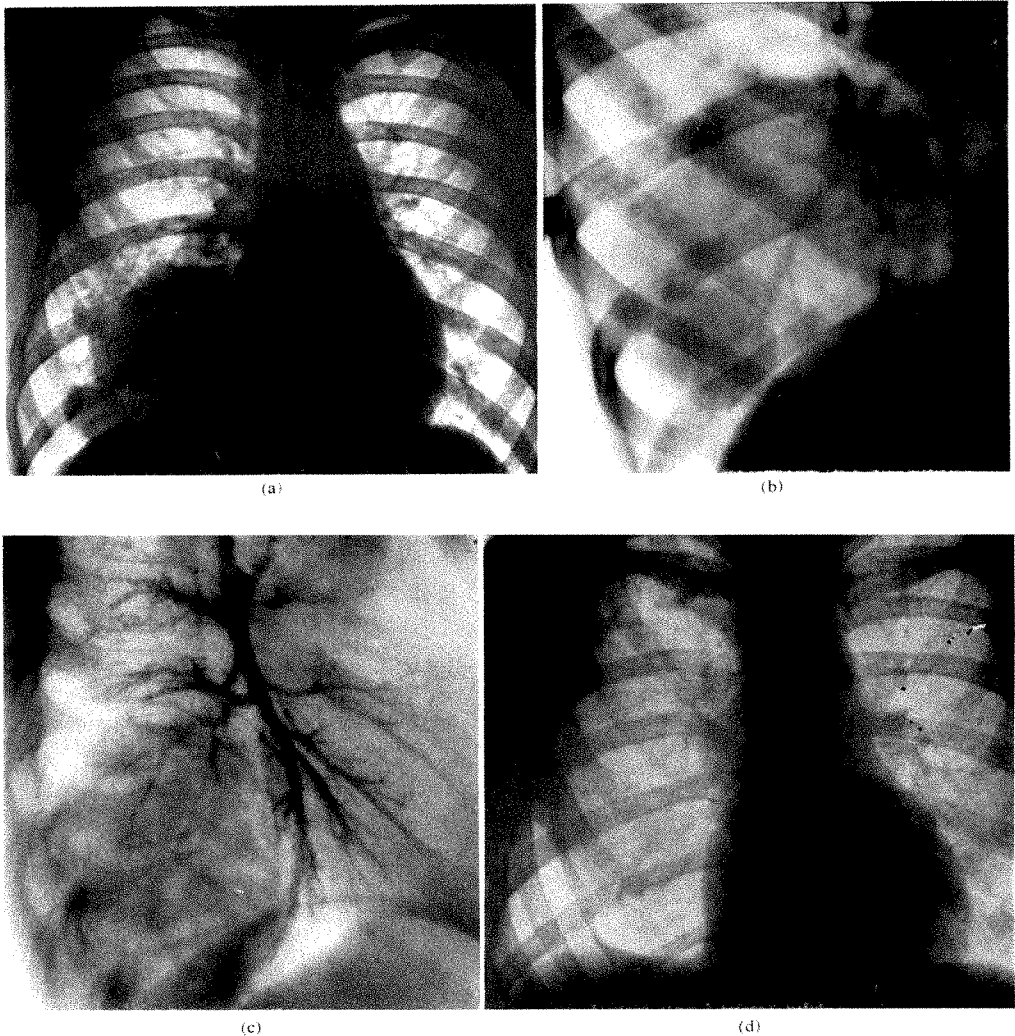


FIG. 3.—Case 2. (a and b) Dense oval shadow in lower posterior part of right hemithorax with presence of two round protrusions and a small fluid level; (c) displacement of bronchi of lower lobe; (d) post-operative radiograph.

columnar and some stratified columnar epithelium, and contained abundant desquamated epithelium, cellular debris and leucocytes. The surrounding area was composed of respiratory epithelium. At the margin of the lobe there was normal lung tissue with functional alveoli.

Case 3. The last patient was a child 14 days old, admitted because she had refused to feed for the past two to three days. Clinical examination revealed the presence of a left diaphragmatic hernia, which was confirmed by radiographs (Fig. 4). Laparotomy was performed, and the stomach, small intestine, part of the

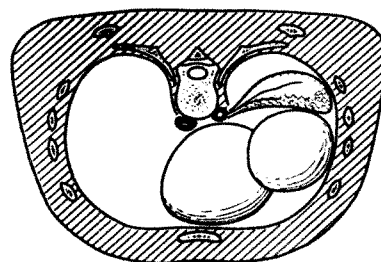
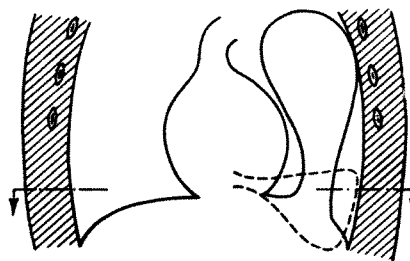


FIG. 5.—Case 3. Diagram showing relationship between diaphragm, hernial sac and accessory lobe.

There was extensive widening of many bronchi. Some groups of alveoli contained foam cells (Fig. 7).

Discussion

Many theories have been advanced about the pathogenesis of this anomaly. The 'traction theory' of Pryce (1946) seems to be the most acceptable. He states that the arterial component is the primary and the malformation of the pulmonary component is secondary. As a result of the persistence of an

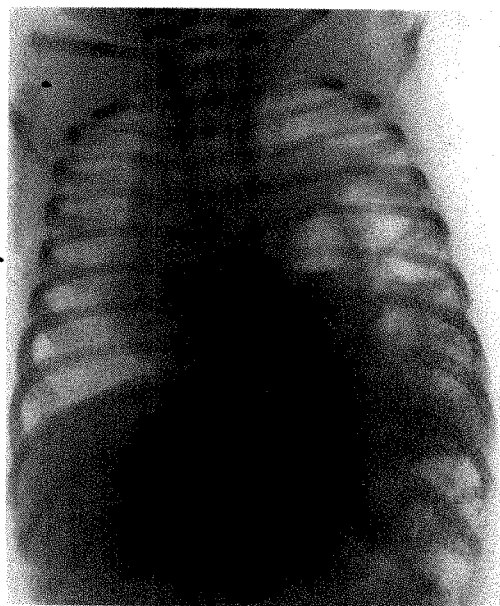


FIG. 4.—Case 3. Shows presence of diaphragmatic hernia on left.

colon and spleen had protruded into the left thorax through a large opening in the diaphragm. They were carefully pulled down. On opening the hernial sac the left lower lobe was found to be rather hypoplastic, but functioning well. On further examination of the left thorax, a small accessory pulmonary lobe-like mass in the posterior costo-diaphragmatic angle was seen. The consistency was that of atelectatic tissue but there was no connexion with the adjacent lung.

Fig. 5 shows the presence of the eventration and its relationship to surrounding structures. Behind the hernial sac is the medial pedunculated accessory lung lobe, which contains an artery arising from the aorta. The mass was removed and the diaphragm was reconstructed by means of the hernial sac membrane. Uncomplicated post-operative progress was verified radiologically (Fig. 6). The child was completely cured.

Microscopical examination showed the presence of bronchi, bronchioles and normal respiratory epithelium.

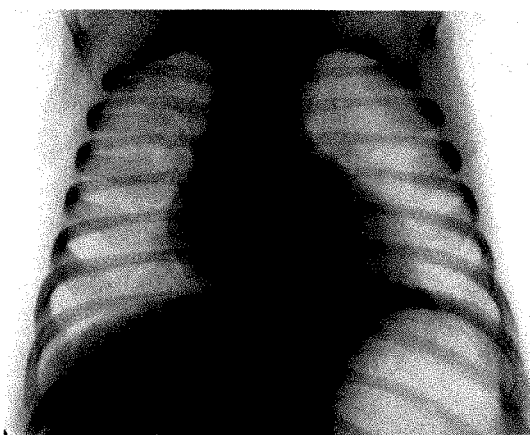


FIG. 6.—Case 3. Twenty-two days after operation.

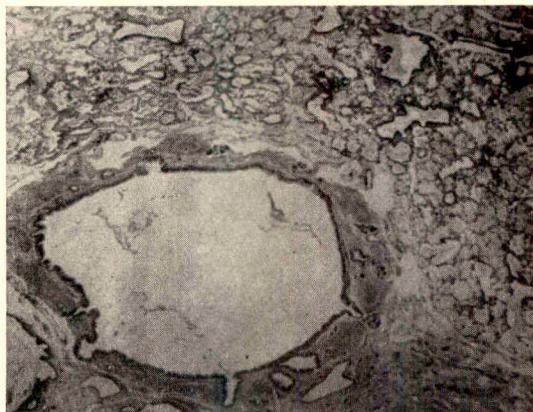


FIG. 7.—Case 3. Histological section showing bronchus, bronchioles and alveoli.

aberrant artery, which supplied a part of the primitive lung lobe, a vascular traction from this lung lobe occurs. The consequence is the dissociation of a piece of pulmonary tissue developed as a sequestration. On the other hand there is the 'fraction theory' which states that pulmonary sequestration develops by abnormal dissociation of a small primitive lung component which seeks an arterial supply from the visceral branch of the aorta itself.

Pulmonary sequestration is composed of respiratory epithelium and ramified bronchi or bronchiectasis without communication with the normal bronchial system. Intralobar sequestration occurs most often in the lower lobe, on the postero-medial aspect. The cases of Cohn and Hopeman (1955), and Warner *et al.* are the only exceptions, because these were found in the upper lobe. Extralobar sequestration is a completely dissociated or ectopic lobe, which can be found above or below the diaphragm. Only in the case of Gruber (1914) was the peduncle attached to the lateral thoracic wall.

The commonest location of extra-lobar sequestration is the left thoracic side and it is related to a diaphragmatic hernia, as in our third case. It is also found in the pericardium and in the abdomen. Location in the right side is rare. Associated anomalies are found, such as congenital absence of

pericardium and communication with the oesophagus. Intralobar sequestration is predominant on the right side and has no relation to other congenital malformations.

With the exception of the complications there is no definite clinical feature of this condition. Sometimes there might be a history of chronic respiratory tract infection, such as productive cough, fever, pleuritic pain, etc. In only a few cases were the patients diagnosed pre-operatively. In most of them the sequestration was found accidentally on radiological examination or at operation. No typical feature appears on the radiograph. However, in a chest film which shows an opacity in the lower lobe and displacement of the bronchi with normal pulmonary findings, we should at least consider this condition. Bronchography is important in the diagnosis, but differentiation from a lung cyst or tumour is not easy. Only in a case of infected pulmonary sequestration can we perhaps see the communication between both bronchial systems on bronchography. Aortography has been suggested by some authors.

Infection of an intralobar sequestration is the commonest complication and is often found. The mode of infection is supposed to be haematogenous. Tuberculosis, malignant change and haemorrhage have also been reported.

The only treatment is operative extirpation of the sequestration. Most authors prefer lobectomy for the intralobar sequestration because removal of the sequestration alone is possible only in exceptional cases. After conservative operation the focus of infection remains in the lung and can spread at any time. Moreover, communication of both pulmonary and aberrant circulations after conservative operation has been observed and an A-V shunt should occur.

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HIATUS HERNIA IN CHILDHOOD*

BY

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The first description of a hiatus hernia was probably that of Bright (1836), who recorded the autopsy of a girl aged 19 years in whom a large portion of the stomach was in the chest and the cardia was at the level of the fourth dorsal vertebra. In the early part of the present century the condition was thought to be rare; Eppinger's (1911) series of 650 diaphragmatic herniae contained only 11 cases of hiatus hernia and in Quénu's (1920) series of 112 cases of diaphragmatic hernia treated surgically there were only two cases of hiatus hernia. With the introduction and development of radiology it was recognized (Åkerlund, 1926) that sliding hiatus hernia, in which the cardia and part of the stomach lie a varying distance above the diaphragm, is the most common form of diaphragmatic hernia and occurs frequently. The condition is found chiefly in the infant and in the middle-aged adult and it has generally been assumed that, in both age groups, similar factors are concerned in the aetiology and the mechanism of production of symptoms. There are, however, significant differences in the clinical features, the natural course of the disease and the response to treatment which suggest that, although the complications may be identical, hiatus hernia in the child is pathogenetically quite distinct from the majority of adult cases.

There is little doubt that infantile hiatus hernia is either present at, or develops shortly after birth; symptoms usually date from the first few days of life and the condition has been demonstrated radiologically during the first week. It was considered by Findlay and Kelly (1931) that hiatus hernia in the child is a congenital, developmental anomaly in which the oesophagus fails to lengthen synchronously with the caudal migration of the septum transversum so that the diaphragmatic hiatus comes to surround the stomach instead of the oesophagus. Botha (1958) thought that a large proportion of hiatus herniae is due to such a developmental short oesophagus. The rapid elongation of the oesophagus in the normal embryo occurs during the

sixth and seventh weeks (Keith, 1948) and a gross anomaly occurring at such an early period of development would be expected to be accompanied frequently by other major abnormalities as is oesophageal atresia which arises about this time. The evidence concerning associated malformations with hiatus hernia is somewhat conflicting, but the reports of multiple anomalies, which include hiatus hernia, have been mostly of isolated cases or of small series (Williams, 1945; Radloff and King, 1947; Barrett, 1950). In our own clinical series of 76 cases no child has a known major congenital abnormality and a low incidence of associated lesions was found by Thomsen (1955) and by Bonham Carter (1956), although mental deficiency was not uncommon in their series.

The anatomical features of hiatus hernia in the child suggest that a developmental shortness of the oesophagus is an unlikely aetiological explanation. The almost invariable presence of a sliding peritoneal sac covering the anterior and left aspects of the intra-thoracic portion of the stomach, the fact that this part of the stomach derives its vascular supply from the coeliac axis and not from the thoracic aorta, and the operative finding that the vagi are not taut and, unless involved in peri-oesophageal fibrosis, do not interfere with reduction of the hernia appear to indicate that the cardia was originally in the abdomen and only later migrated into the chest. In the acquired hiatus hernia of the adult, in which the pathological anatomy is identical with that of the child, an important aetiological factor in most cases, and the primary one in many, is relaxation of the diaphragmatic hiatus due to degenerative changes in the musculature. Barrett (1954) and Forshall (1955) have therefore considered that the essential lesion in the infantile case is a congenital weakness or laxity of the hiatus which allows herniation of the cardia shortly after birth when a negative intra-thoracic pressure develops with the onset of respiration. An objection to this hypothesis is that hiatus hernia in the child can undergo gradual spontaneous reduction (Figs. 1 and 2) and eventual cure; spontaneous recovery of

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

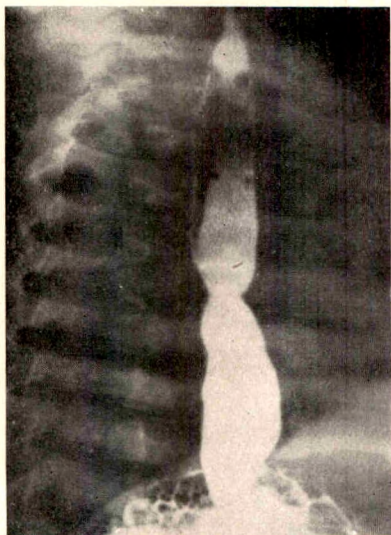


FIG. 1.—Long, tubular hiatus hernia in child aged 3 months. Cardia at level of sixth dorsal vertebra.

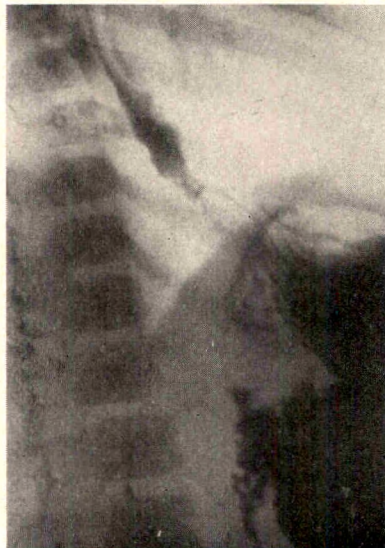


FIG. 2.—Same patient as in Fig. 1, aged 18 months. Symptomless. Marked spontaneous reduction in size of hernia.

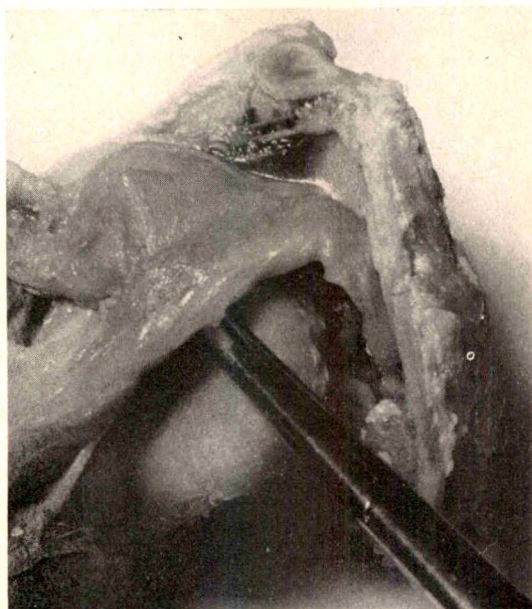


FIG. 3.—Autopsy specimen of hiatus hernia in still-born anencephalic infant. Forceps in sliding peritoneal sac



FIG. 4.—Same specimen as in Fig. 3. Stomach and cardia withdrawn from above diaphragm, demonstrating sliding sac.

a diaphragmatic weakness, if possible at all, would be unlikely to lead to the reduction of a large hernia. The autopsy finding of a hiatus hernia in a still-born anencephalic infant indicates that a pressure difference between the abdomen and the thorax is not an essential pathogenetic factor. The gross associated anomaly in this case at first suggested that the condition was a 'congenital short oesophagus' but dissection revealed the typical anatomical features of a sliding hernia (Figs. 3 and 4). As the child had never breathed, the cardia must have become displaced during pre-natal life.

An important agent in the production and maintenance of some cases of adult hiatus hernia is pressure from below, displacing the cardia upwards through the hiatus; symptomatic and even radiological cure may follow reduction of intra-abdominal pressure by the elimination of obesity, the abandonment of corsets or the evacuation of a pregnant uterus (Dutton and Bland, 1953). There is no evidence of an unduly high intra-abdominal pressure in the infant with hiatus hernia but the not infrequent association with hypertrophic stenosis of the pylorus, the phreno-pyloric syndrome of Roviralta (1952), suggests that raised intra-gastric pressure or increased gastric peristalsis may similarly force the cardia into the chest. The coincidence of pyloric stenosis in our hiatus hernia series is 10.5%. In Bonham Carter's (1956) series of 136 cases of hiatus hernia five children had pyloric stenosis and he suggested that the vomiting caused by the latter leads to the development of the hernia when there is a congenital laxity of the oesophageal hiatus. In our eight patients with the double lesion, however, vomiting began shortly after birth and not, as occurs with pyloric obstruction alone, after the second week of life.

The pathogenesis of hypertrophic pyloric stenosis remains unknown. Thomson (1933) considered that the muscular hypertrophy of the pyloric canal occurs as a result of a preceding functional obstruction at the pyloric sphincter. Friesen, Boley and Miller (1956) claim to have demonstrated immaturity of ganglion cells in the pyloric tumour. As pyloric stenosis, unlike hiatus hernia, occurs predominantly in the male and has a high familial and hereditary incidence, there is obviously no all-embracing aetiological explanation for the two conditions but their frequent co-existence lends support to Thomson's theory of a prenatal functional pyloric obstruction; the increase in intragastric pressure so produced may then lead to prolapse of the cardia into the chest especially since, at this period of development, the gastro-oesophageal junction is probably not yet stabilized in its normal position.

Some of the clinical features of infantile hiatus hernia, even when there is no associated hypertrophic pyloric stenosis, also suggest the presence of a gastric emptying disorder. That the hernia and the incompetent cardia, although responsible for the development of oesophagitis, are perhaps not the primary cause of the main symptom of vomiting is indicated by the fact that, in those children treated medically and in many of those treated surgically, the hernia and gastro-oesophageal reflux may still be demonstrable radiologically many months after vomiting has ceased. Interference with gastric emptying is suggested by the frequent clinical finding of visible gastric peristalsis and by the fact that the vomiting itself, unlike the passive postural reflux of a small quantity of gastric contents which occurs in the adult, is usually forcible or even projectile, of large volume and not immediately controlled by postural treatment.

Medical management of hiatus hernia in infancy is often successful in relieving the symptoms and in allowing spontaneous cure of the hernia and the development of a competent gastro-oesophageal sphincter. The disadvantage of conservative management is that hospital treatment must often be prolonged, and it is difficult to decide when the patient may be considered free of the risk of complications developing. It is often considered that cure has been achieved when vomiting ceases and the child gains weight normally. The hernia and the incompetent cardia persist, however, for some considerable time after vomiting has stopped and the symptomless patient may still be exposed to the risks of oesophagitis and its sequelae. Severe complications, if they are going to occur, usually develop early but this is not invariably the case; in one of our patients an oesophageal stricture first appeared at the age of 10 years (Figs. 5 and 6). Chronic penetrating ulcer of the intra-thoracic portion of the stomach (Barrett's ulcer) may also develop in later childhood (Fig. 7).

The conventional surgical procedure for hiatus hernia in the child, as in the adult, is transthoracic, transdiaphragmatic reduction of the hernia and repair of the enlarged oesophageal hiatus. In our experience of 40 cases this operation has not given satisfactory results; vomiting has persisted after operation in over 50% of patients and radiological examination, carried out one year or more after operation, has shown recurrence of the hernia or persistence of gastro-oesophageal reflux in over 70%. Unsatisfactory results of hiatal herniorrhaphy in childhood have also been recorded by Husfeldt (1953) and by Thomsen (1955).

Although there is no radiological confirmation of

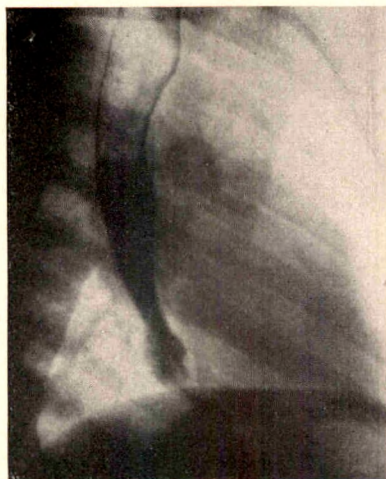


FIG. 5.—Hiatus hernia without stricture in boy aged 6 years.

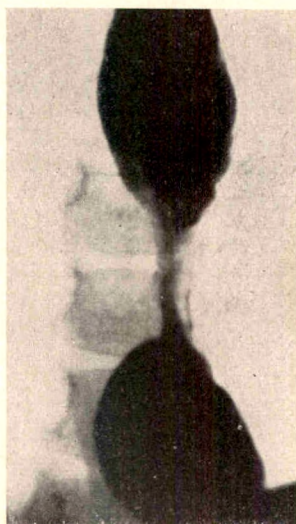


FIG. 6.—Same patient as in Fig. 5, aged 10 years. Severe oesophageal stricture.

a gastric emptying disorder in cases of infantile hiatus hernia, there would appear to be sufficient clinical evidence of its temporary presence, responsible at least in part for the development of the lesion and the production of the symptom of vomiting, to justify the therapeutic application of this hypothesis. The operation of pyloroplasty has therefore been applied to the treatment of hiatus hernia in childhood. The rationale of this procedure is that facilitation of gastric emptying will discourage

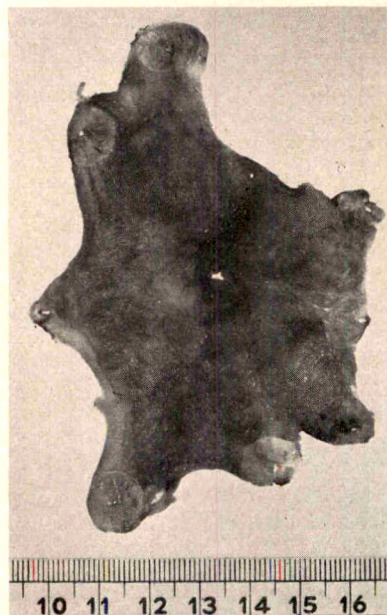


FIG. 7.—Operation specimen. Chronic penetrating peptic ulcer (Barrett's ulcer) of intra-thoracic part of stomach in boy aged 9 years with recurrent haematemesis.

vomiting and encourage spontaneous cure of the hernia and the development of a competent gastro-oesophageal sphincter. Peptic oesophagitis is due to reflux of pepsin and acid from the stomach; the most severe effects are probably produced by reflux of unbuffered gastric juices when the stomach is empty of food. In order to inhibit this neurogenic peptic secretion and so render inert fluid regurgitating into the oesophagus, bilateral vagotomy has been performed in addition to pyloroplasty when endoscopy revealed the presence of oesophagitis. These procedures have so far been applied to only a small series of cases. The early response has been satisfactory but more prolonged study of the patients is required before full assessment of the results is possible.

Summary

The pathogenesis of infantile hiatus hernia is discussed. It is considered that an important factor in the causation of the hernia and in the production of vomiting is a disorder of gastric emptying. The operation of pyloroplasty and, in the presence of peptic oesophagitis, vagotomy has therefore been carried out in a small series of cases.

I am grateful to my colleagues Miss Isabella Forshall and Mr. P. P. Rickham and to the paediatric physicians

of the Liverpool Region who have permitted me to examine their patients. I am indebted to Dr. E. G. Hall for the use of autopsy material.

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TEMPERATURE CHANGES DURING NEONATAL SURGERY*

BY

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My subject is temperature changes occurring during neonatal surgery. My interest in this subject was stimulated by the obvious cooling which occurred during neonatal operations, the absence in current practice at Great Ormond Street of any special measures to prevent this loss, and the varied methods of rewarming in practice. Also there occurred one or two cases of post-operative sclerema, and it seemed worth while to investigate this temperature loss more fully.

In the past six months or so I have recorded the temperatures, at 10-minute intervals, of 25 infants during operation. Temperatures have been recorded in all cases by a Thermocouple calibrated against an alcohol thermometer reading over the range 20-40° C. and the lead has in all cases been placed in the rectum, except on the two occasions when this would have interfered with the operation. An oesophageal lead was then used. The oesophageal temperature has usually been found, on the occasions when both readings have been taken, to be somewhat higher than the rectal, but the same rate of drop has occurred.

The infants are divided into two groups: in the first 14 the existing practice was followed, no measures being taken to prevent heat loss, and in the next 11 cases the limbs and trunk, apart from the operation site, were insulated with cotton wool held in position by crepe bandages. On later analysis of the type of operations performed it was found that these two groups could fairly be compared.

The average time of operation was 80 minutes and the average temperature loss in the control group was 2.31° C. and in the insulated group 1.56° C. (Table 1). The following are some graphic records of these infants, all of whom were less than 7 days old.

In the control group the greatest loss recorded was in a 6-day-old infant with a diaphragmatic

hernia which was reduced through an abdominal approach. She had a good initial temperature and lost 4° C. in 100 minutes (Fig. 1).

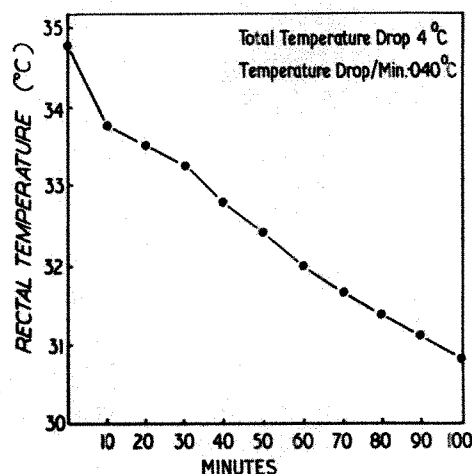


FIG. 1.—J.H., aged 6 days, birth weight 7 lb. 1 oz. Diagnosis: right diaphragmatic hernia.

A characteristic chart is shown in Fig. 2. This is an oesophageal temperature recording, as the baby was having a 'pull-through' operation for anorectal agenesis. There was quite a good initial temperature with a steady loss thereafter until the peritoneum was closed, when there was a slight elevation.

TABLE 1
NEONATAL TEMPERATURE LOSS
(TOTAL CASES RECORDED 25)

Group 1		Group 2	
Controls	14	Insulated	11
Average temperature loss 2.31° C.		Average temperature loss 1.56° C.	
Average length of operation 80 mins.			

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

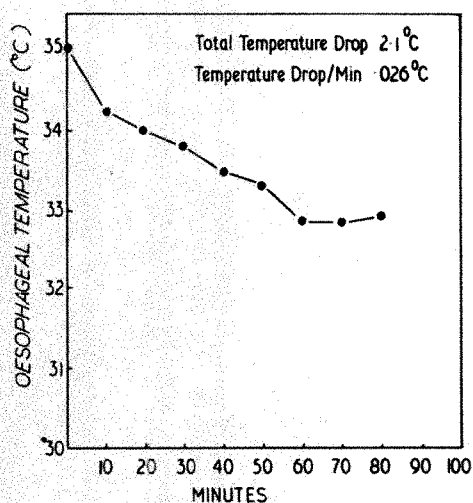


FIG. 2.—A.M., aged 12 hours, birth weight 6 lb. Diagnosis: anorectal agenesis.

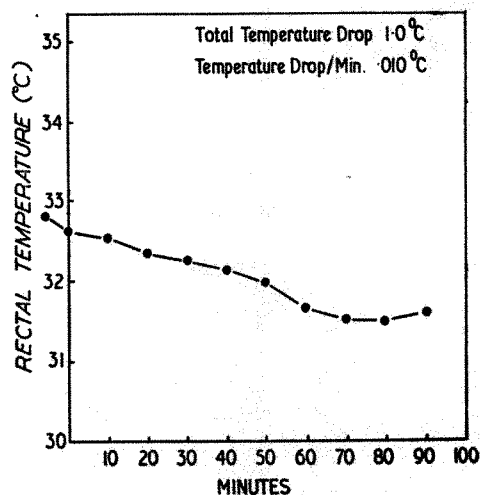


FIG. 4.—F.D., aged 3 days, birth weight 4 lb. 2 oz. Diagnosis: jejunal atresia.

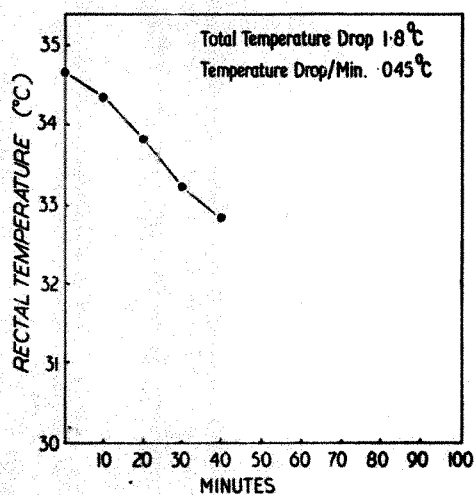


FIG. 3.—S.T., aged 1 day, birth weight 6 lb. Diagnosis: diaphragmatic hernia.

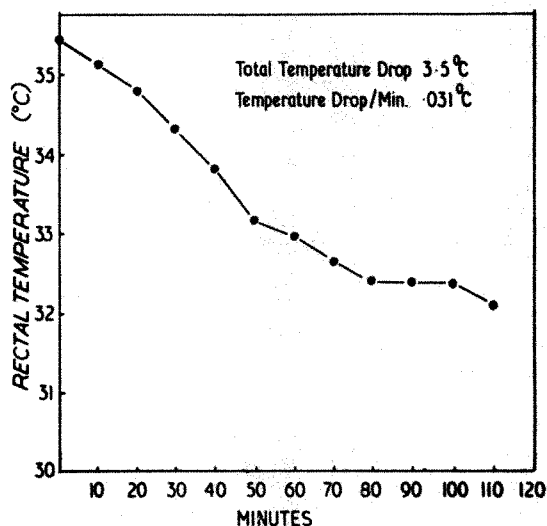


FIG. 5.—S.W., aged 5 days, birth weight 6 lb. 14 oz. Diagnosis: oesophageal atresia.

Fig. 3 is from another child with a diaphragmatic hernia which was again reduced through the abdomen, although rather more easily than in the first child. This chart shows well the marked and steady temperature drop, the loss being 1.8°C . in 40 minutes. Owing to the diminished differential between the temperature of the child and its environment, it was found, not surprisingly, that the lower the infant's initial temperature, the less the total drop, although the loss does continue (Fig. 4).

There were four cases of oesophageal atresia in the control group. Fig. 5 shows one of these. The temperature losses in these four cases were 1.7°C ., 2.6°C ., 2.6°C . and 3.5°C .

In the second group of cases, which were insulated, there were three cases of oesophageal atresia. Their temperature losses at operation were 1.6°C ., 1.4°C . and 1.2°C ., and the chart of one of them (Fig. 6) illustrates well the difference in rate of temperature loss. The operation here was rather

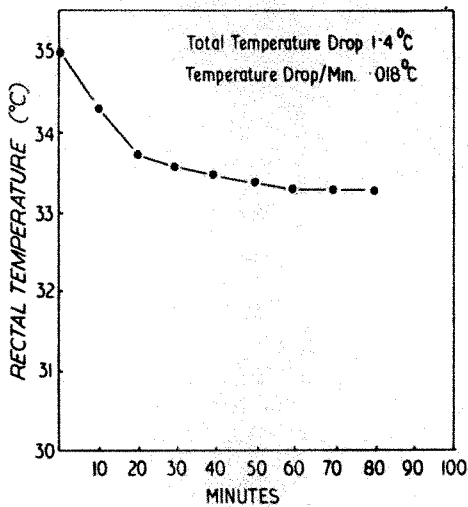


FIG. 6.—D.S., aged 18 hours, birth weight 6 lb. 3 oz. Diagnosis: oesophageal atresia.

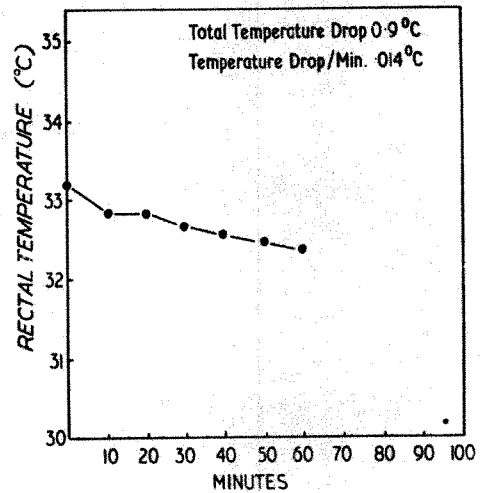


FIG. 8.—L.M., aged 2 days, birth weight 4 lb. Diagnosis: ileal atresia.

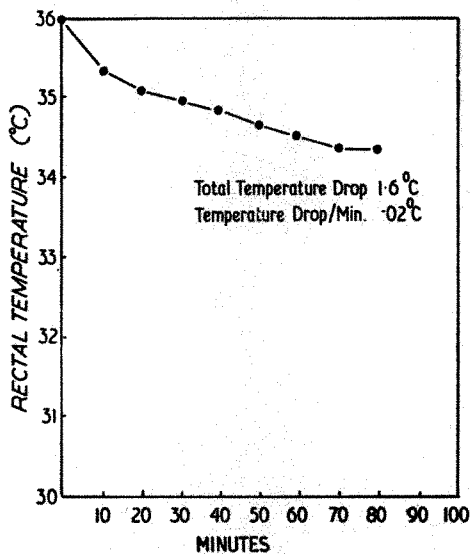


FIG. 7.—D.G., aged 3 days, birth weight 5 lb. 11 oz. Diagnosis: oesophageal atresia.

shorter than that of the previous case in the control group, but the temperature loss in 80 minutes was 1.4° C. whereas in the uninsulated child it was 3.2° C. in the same time.

A representative chart in the insulated group is of one of the other cases of oesophageal atresia (Fig. 7). This baby had a good initial temperature: there was the initial loss in the first 10 minutes and the loss thereafter was well controlled. Finally

an impressive recommendation for insulation is the chart (Fig. 8) of a 4 lb. (1,800 g.) infant operated upon for ileal atresia. In 65 minutes the total temperature loss was only 0.9° C. The figures of all the recordings are shown in Figs. 9 and 10. In the control group the loss per operation averaged 2.31° C., or 0.033° C. per minute, and in the insulated group the average loss was 1.56° C. or 0.02° C. per minute.

Points which arose during these recordings were:

(1) In several cases there was a considerable temperature drop between the time the child was brought into the theatre and removed from the incubator and the time the operation was commenced. Such temperature loss can, and should be, avoided.

(2) The diathermy electrode pad used during these operations measured 10 × 7 cm. The lead plate is enclosed in a cover soaked in saline, and placed under the baby's sacrum. The size of this plate could safely be reduced if especial care were taken in applying the pad, which should be kept unbent; the use of electrode jelly might also help to diminish temperature loss.

(3) Records were taken during these operations of conditions in the theatre. The average theatre temperature was 24.5° C. (76° F.) with a range of 20-26.7° C.; the average relative humidity was only 50% with a range of 41-64%; the number of persons present in the theatre varied from a minimum of seven to a maximum of 17. The ventilation system during all but one of these operations was changing the theatre air 17 times an hour. A

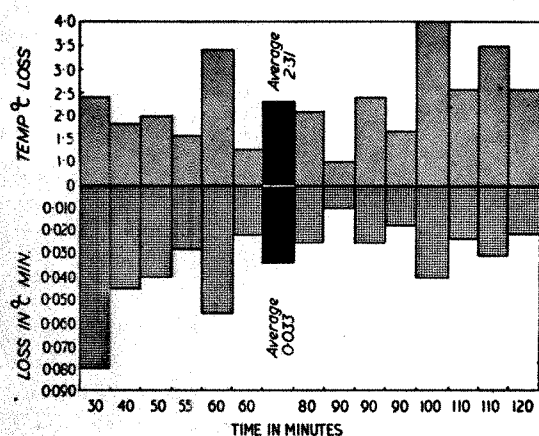


FIG. 9.—Figures of all the recordings in the control group.

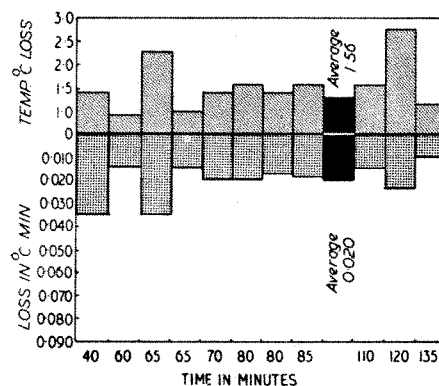


FIG. 10.—Figures of all the recordings in the insulated group.

higher environmental temperature and humidity will reduce heat loss and a temperature of 26.5°C . (80°F .) is not too unpleasant for the surgeon or theatre staff.

The question which, of course, arises is whether temperature loss in these newborn infants matters. Twenty-five cases is too small a series from which to draw any conclusions, but there was no significant difference noticed in the post-operative courses of the infants in these two groups. A vast amount of research has been undertaken of late into hypothermia and its effects, but I venture to suggest that the problem as referable to a newborn baby—and not infrequently a premature baby as well—is rather different from that in older children or adults. We take great care to maintain the temperature of our newborn babies post-operatively (at Great Ormond Street they are almost all nursed in incubators), and it seems irrational not to try to prevent heat loss at operation.

Silverman, Fertig and Berger (1958) reported the result of an investigation to determine the effect of temperature on the survival rates of premature infants. Their results confirmed the view that survival rates can be increased by reducing the heat loss of such infants in the first few days of life. Many neonatal surgical emergencies occur in premature infants, and for full-term infants it seems not unreasonable to suggest that heat conservation is also important. The more premature the infant the more inefficient is its temperature regulating mechanism; a normal baby also has a relatively immature regulating mechanism but after several days, perhaps a week, this mechanism has adapted itself to meet the needs of its new environment. The factors involved in this inability to regulate temperature are the immaturity of the centre itself—Brock

called this 'lack of practice' (Ungeübtheit); the inadequacy of the vasoconstriction and shivering mechanisms; and a relatively large surface area with a small amount of subcutaneous fat, both predisposing to excessive heat loss. On the heat production side it is worth mentioning that although the infant's basal metabolic rate is higher than the adult's, using body weight as a criterion, it is lower when estimated against surface area, and this is even more marked in the premature infant (Smith, 1951).

Rickham (1957) mentioned that in his series no active means were taken at operation to maintain the body temperature and listed three theoretical objections to heating the subject at operation, namely (a) that peripheral vasodilation may have the effect of depriving the vital centres of blood flow, (b) that a low temperature decreases the oxygen need by reducing the metabolic rate, and (c) that hypothermia increases neonatal resistance to anoxia.

Peripheral vasodilation is certainly undesirable and it should be remembered, in this context, that it is as easy to overheat an infant as to overcool it. I do not feel that the other two objections offer sufficient justification for allowing a large operative temperature drop.

A brief word about sclerema, the condition characterized by a yellowish-white skin which has a firm resistant feel, which does not pit on pressure and which is fixed to underlying bone and muscle. One case in this series developed the condition. This very ill baby had had a laparotomy elsewhere for intestinal obstruction. He was transferred to Great Ormond Street, was thought to have gastro-enteritis and possibly septicaemia in addition to his obstruction, and at re-operation required a colostomy for Hirschsprung's disease. He was treated with intravenous hydrocortisone immediately post-operatively

as a resuscitative measure. In spite of this he developed gross sclerema. The hydrocortisone was continued and he happily, and somewhat surprisingly, recovered. His initial temperature was 36.4°C . (97.5°F .), his limbs were padded and he lost only 1.4°C . during the operation. Excessive cooling does seem, from reports, to predispose to the development of sclerema, but it seems as if quite frequently, and possibly always, an infective process is involved also.

The conclusions which may be drawn from these investigations therefore are:

(1) Infants at operation may lose a considerable amount of heat. The full biochemical implications of this heat loss are at present unknown, but it is the opinion of one authority at least (Payne, 1959) that they are probably not very important. The effect on the infant's respiration is more immediately important and more easily appreciated. The hypothermia may appreciably delay the return of adequate respirations and predispose to post-operative chest complications.

(2) It is possible to reduce this temperature loss by one-third by the simple expedient of wrapping the infant in cotton wool. A higher theatre temperature than is customary has also been shown to diminish loss.

(3) In the latter part of this series, using insulation and a high environmental temperature, the total loss was reduced by 1°C .- 1.4°C . in several cases.

(4) It seems that if these measures are adopted, active heating by hot water bottle or electric blanket, which has to be carefully controlled during operation, is probably unnecessary.

(5) In view of the expected temperature loss during operation an infant whose temperature is initially low, especially one suspected of having any degree of infection, should probably be warmed before operation is undertaken in order to diminish the risk of development of sclerema neonatorum.

I would like to thank Professor A. W. Wilkinson for the interest he has shown and the helpful criticism he has offered me, both during this investigation and in the preparation of this paper. My thanks are also due to Mr. G. Lythe, of The Hospital for Sick Children, for his help in preparing the figures in this paper.

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INCUBATOR FOR INFANTS UNDERGOING SURGERY*

BY

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For the last six years all infants operated upon in the Neonatal Surgical Unit at Alder Hey Children's Hospital have been nursed in incubators during the immediate pre- and post-operative period. The infants are nursed at a constant temperature of 85° F. (29.5° C.). Draughts and sudden changes in temperature are thus prevented and the infants can be nursed naked. The rate and type of respiration can be constantly watched, the abdomen can always be inspected and the child can move freely and unrestrained by clothing. If necessary he can be nursed in a definite concentration of oxygen, which is important in cases with pulmonary collapse, pneumonia or abdominal distension. The infants are nursed in an atmosphere of 100% humidity, which, in our experience, is the most important single factor in the prevention of post-operative pulmonary complications, as it liquifies the sticky pulmonary secretion, thus preventing blocking of the bronchi and pulmonary collapse (Rickham, 1957a).

It has been shown by O'Brien, Hansen and Smith (1954) that newborn infants nursed under the atmospheric conditions described above have an insensible water loss less than half that of infants nursed at room temperature and humidity. The high atmospheric humidity not only reduces water loss to a marked degree, but it also makes any metabolic balance studies which may be carried out much more accurate, since at a temperature of 88° F. (31° C.) and 100% humidity the daily water loss remains constant at 13.8 g. per kg. of body weight (Rickham, 1957b).

Nursing in incubators is even more important for premature infants undergoing surgery than for full term babies. Premature infants stand a fall in body temperature very badly and require to be nursed at incubator temperatures of between 90° and 95° F. (32° to 35° C.). Any marked drop in body temperature in premature infants undergoing surgery predisposes to sclerema, the development of which may prove fatal (Rickham, 1957c).

Experience gained in the nursing of surgical newborn babies during the last 10 years has shown that the incubators in use for premature infants in medical paediatric practice are not very suitable for newborn babies undergoing operations. These children should be brought to the operation table in an incubator and should after operation be lifted off the table and returned to the incubator. Procedures such as examinations, obtaining blood samples, setting up intravenous infusions, sucking out the pharynx, passing stomach tubes, endotracheal intubation and artificial respiration should be carried out in the incubator with the minimum disturbance of the infant. An incubator which is employed to transport babies to and from the operating theatre must be provided with oxygen supply and drip stands.

A number of infants admitted to the unit for operation have been submitted to balance studies necessitating careful intake and output estimations and accurate daily weighing. Considerable disturbance was caused to the babies by these investigations when ordinary incubators were in use.

It was decided to modify a standard incubator so that it would fulfil the requirements mentioned above. The Mark IV incubator made by Messrs. Oxygenaire, Ltd., London, was chosen for this purpose. The modified incubator has now been in use for several months and has proved very satisfactory.

The Mark IV incubator contains no electric motor, air circulation being produced by thermal convection. The absence of a motor eliminates many causes of mechanical breakdowns. Apart from the usual humidifying mechanism, a built-in atomizer (Fig. 1) permits the raising of the atmospheric humidity to 100% within a few minutes. Warm dry air circulates behind the front panel preventing misting due to humidity and allowing the infant to be watched at all times. Even with an oxygen inflow of 6 litres per minute the oxygen concentration in the incubator cannot rise above 35%; with the usual practice of allowing 1½ litres per minute, the concentration is 26%. There is a slight positive

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

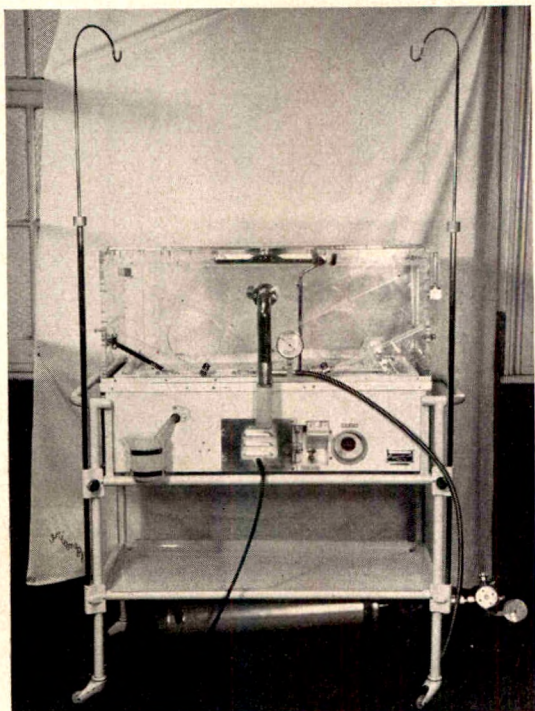


FIG. 1.—Rear view showing atomizer in centre and receptacle for urine on left side. Note adjustable drip stands and oxygen cylinder carrier.

FIG. 2.—Front view showing large sliding doors. Plastic cradle is suspended from weighing machine. Note metal buckles at edge of plastic cradle.



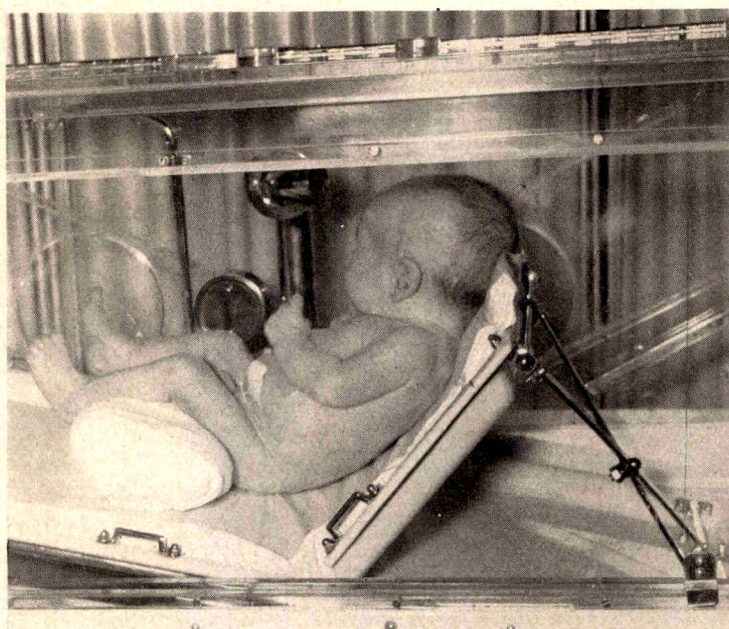


FIG. 3.—Infant nursed in semi-sitting position on adjustable backrest.

pressure in the incubator, so that opening it does not cause air to rush in.

In the modified surgical model the front panel is composed of two horizontally sliding doors, which when open give the widest possible access. The groove in which the sliding doors run is just below the level of the tray on which the infant lies so that the infant can be handled without discomfort to the nurse's arms.

The child is nursed on a plastic, radio-translucent cradle, which can be tilted into Trendelenburg's and anti-Trendelenburg's positions. Six metal buckles are fixed along the edge of the cradle and it is thus possible to immobilize the baby in various positions by tying the limbs to the buckles (Fig. 2). In order to nurse the infant in a semi-sitting position, which may be necessary for such conditions as hiatus hernia, an adjustable backrest is incorporated (Fig. 3). Radiographic pictures are taken by placing the photographic plate underneath the plastic cradle on a metal tray which can be pulled out through a hinged panel situated on the left side of the incubator. In order to facilitate accurate placing of the cassette beneath the infant, the metal tray is divided into numbered squares corresponding to numbers painted on the side of the plastic cradle. The cassette is fixed securely to the tray with the aid of a metal bar attached to two rubber suction pads (Fig. 4).

On the right side of the incubator there is a hinged

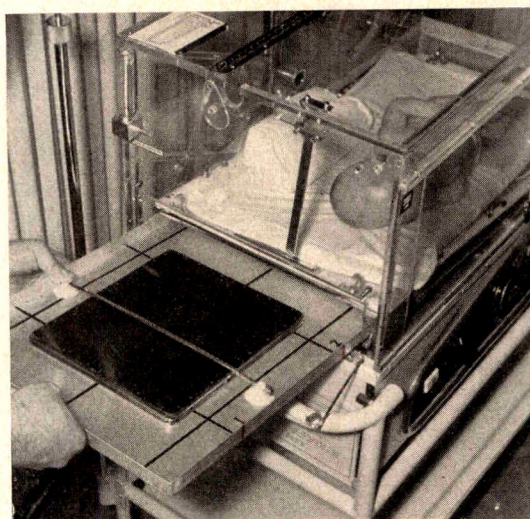


FIG. 4.—Left side panel. Metal tray pulled out and radiographic cassette fixed in position by metal band suction pads. Note drip feed apertures.

panel 6 in. in height (Fig. 5). With this flap open, various procedures can be performed. On admission the infant is placed into the incubator with his feet pointing towards this panel. When an intravenous infusion is set up in the ankle the child's feet are pulled out of the incubator through this opening (Fig. 6).

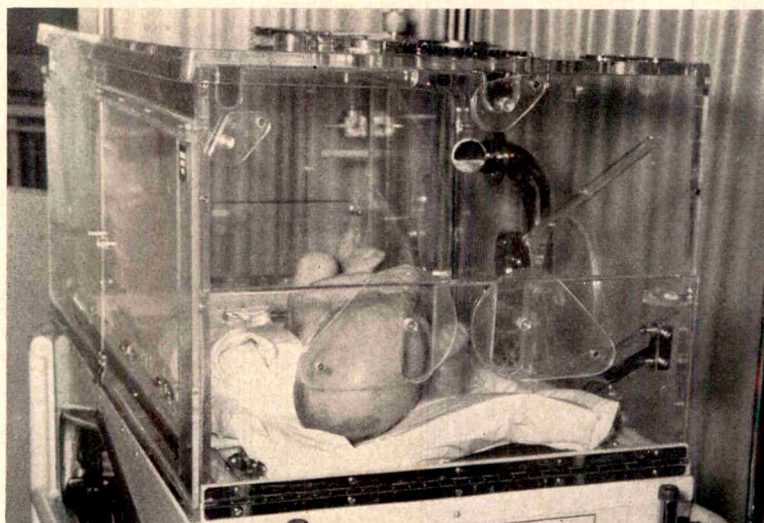


FIG. 5.—Right side panel showing large hinged flaps with deep slots guarded by plates cut into upper border.

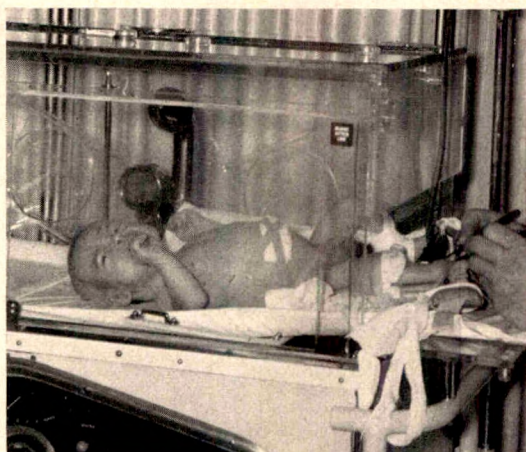


FIG. 6.—Intravenous infusion is set up in internal saphenous vein at right ankle.

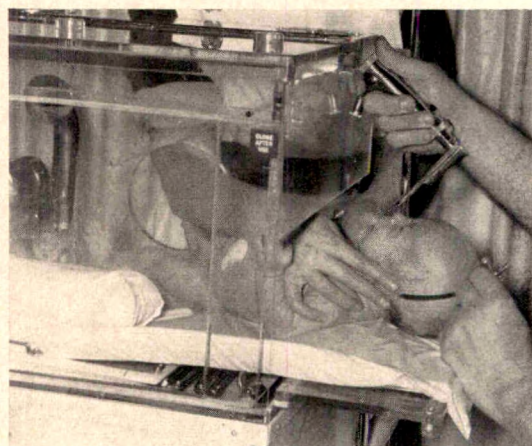


FIG. 7.—Endotracheal intubation.

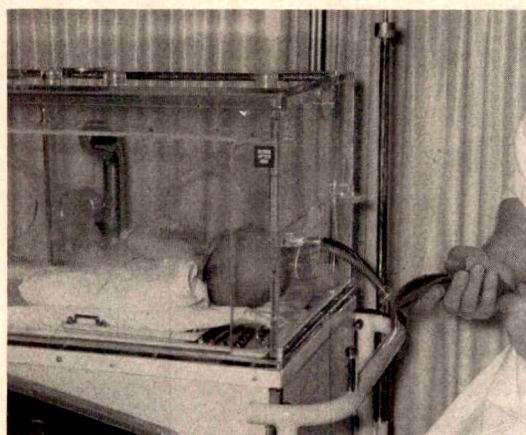


FIG. 8.—Artificial respiration given by endotracheal intubation.

Following the operation the infant is put back into the incubator with the head pointing towards the flap. Procedures such as emergency intubation (Fig. 7) and putting up of scalp vein infusions are thus easily carried out. Prolonged positive pressure artificial respiration is facilitated by passing the oxygen tubes through the deep slots cut into the hinged flap (Fig. 8).

There are four holes for suction drainage tubes along the lower edge of each side panel. The urine of male infants is collected by fixing a piece of Paul's tubing around the penis and passing it through an opening in the metal panel at the back of the incubator to a receiver.

The incubator is provided with two adjustable drip-stands fixed one to either side and an oxygen

cylinder carrier slung beneath the bottom shelf (Fig. 1).

The infant can be weighed in the incubator without much disturbance by suspending the cradle on which he lies from an accurate weighing machine placed on top of the upper lid (Fig. 2).

We should like to record our thanks to Miss Isabella Forshall, Dr. J. G. Rees and Dr. A. L. Stead for their most helpful suggestions. The expert advice and generous help of Mr. S. Sullivan and Mr. F. Crosdail of Oxygenaire Ltd. have been invaluable in the planning of this incubator.

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DEVELOPMENTAL POSTERIOR ENTERIC REMNANTS AND SPINAL MALFORMATIONS*

THE SPLIT NOTOCHORD SYNDROME

BY

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From the Royal Hospital for Sick Children, Glasgow

Clinicians have only recently recognized the aetiological factors that connect a wide variety of developmental anomalies of the skin of the back, the spine, the central nervous system and the gut (Beardmore and Wigglesworth, 1958; Nathan, 1959). Starting with the observations of Lereboullet (1863) on the formation of sagittally split embryos from artificially inseminated pike ova, evidence has slowly accumulated which shows their common origin from a single aberration of development.

The many publications in the intervening years dealing with these apparently dissociated malformations have been difficult to correlate, due to variations in both terminology and suggested aetiology. The purpose of this paper is: (i) To summarize the embryological background to the concept of the split notochord syndrome; (ii) to suggest a generic title for the group of anomalies and a nomenclature for the gut components; (iii) to describe five illustrative cases; and (iv) to give key references to the relevant literature.

The split notochord syndrome embodies lesions that have been described under the following titles:

Anterior and combined spina bifida; 'butterfly vertebra'; diastematomyelia; diplomyelia; Klippel-Feil syndrome; accessory or persistent neurenteric canal; dorsal intestinal fistula; spinal and cranial cysts; post-vertebral 'teratomatous' or dermoid cysts and sinuses; pre-vertebral, mediastinal or mesenteric cysts; some enteric 'duplications' or diverticula; vesico-intestinal fissure and certain intestinal malrotations and diaphragmatic herniae.

Embryology

An embryo may develop with partial duplication and separation of the notochord, the level and

extent of the separation being variable; this results in a gap developing in the dorsal tissue mass between the two parts of the notochord (Figs. 1 and 2). Through this gap the ventrally situated yolk sac or gut anlage endoderm will herniate and it eventually adheres to the dorsal ectoderm or skin anlage (Figs. 3 and 4). The hernia may rupture to produce a fistula from the yolk sac into the amniotic cavity which separates the halves of the future cord and spine (Fig. 5). Subsequent differential growth of the embryo tends to close and obliterate the fistula and the extent of residual lesions depends on the success attained by this process. Thus the development of the base of the skull, vertebral column and central nervous system may be affected as well as gut, while sequestration of dorsal ectoderm may lead to dorsal dermoid cysts and sinuses. Persisting remnants of yolk sac origin may differentiate into tissues characteristic of any part of the gut or its embryological derivatives such as lung, etc. (Figs. 6, 7, 8, 9). Differential growth of gut and vertebral column leads to wide separation of the areas affected in each, as in long diverticula originating within the abdomen and passing through abnormal openings in the diaphragm to a high thoracic vertebral attachment. Furthermore, abnormal fixation of gut to the vertebral column may cause subsequent failure of rotation.

Clinical Presentation

Hitherto all the consequent malformations have been considered individually as extreme rarities, but if they are grouped the basic pattern is found to be fairly common.

These malformations may be considered to fall into two broad classes: (a) visceral malformations, and (b) spinal and central nervous malformations.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

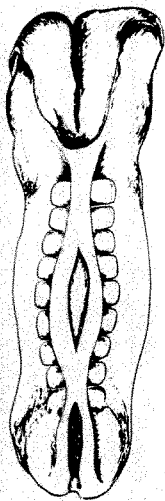


FIG. 1.—Anomalous embryo (2 mm.) with split notochord ('ring embryo').

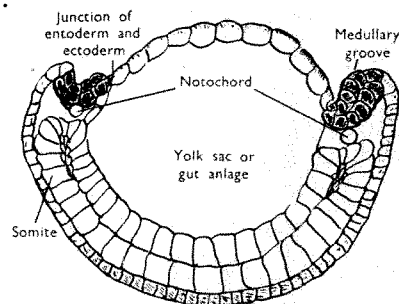


FIG. 2.—Section across anomalous embryo with split notochord.

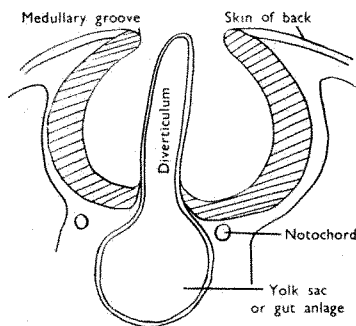


FIG. 3.—Posterior diverticulum of yolk sac developing between split elements of notochord.

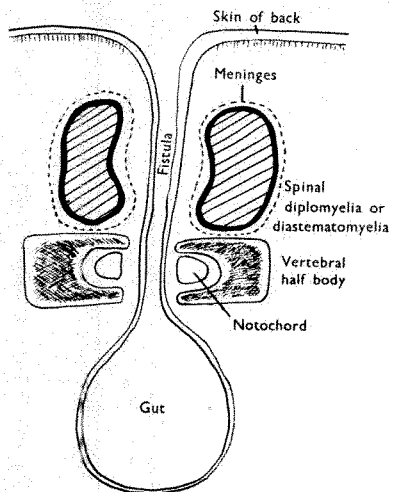


FIG. 4.—Early stage in evolution of developmental posterior enteric fistula.

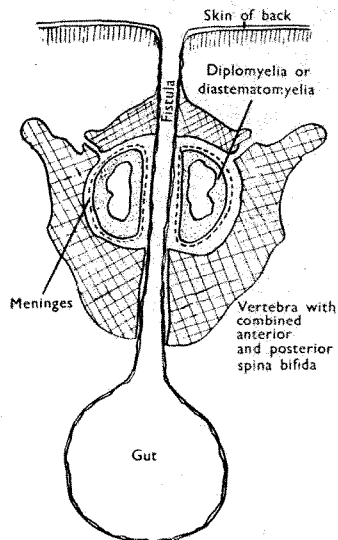


FIG. 5.—Established developmental posterior enteric fistula.

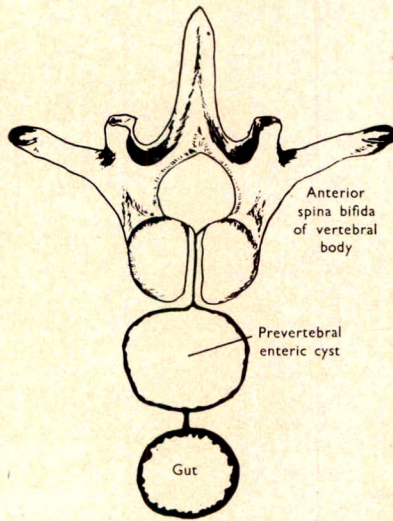


FIG. 6.—Prevertebral developmental posterior enteric cyst.

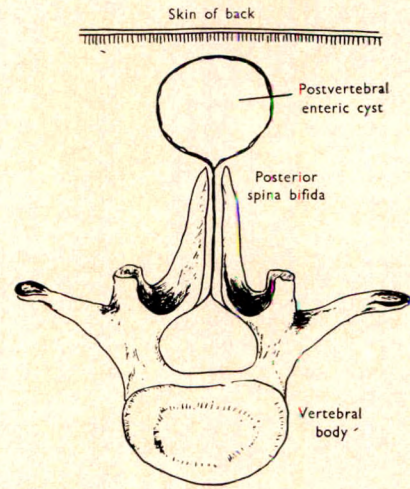


FIG. 7.—Postvertebral developmental posterior enteric cyst.

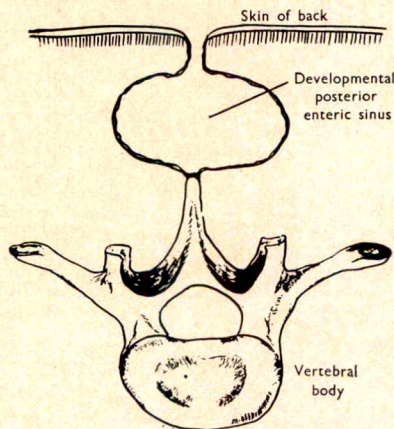


FIG. 8.—Developmental posterior enteric sinus.

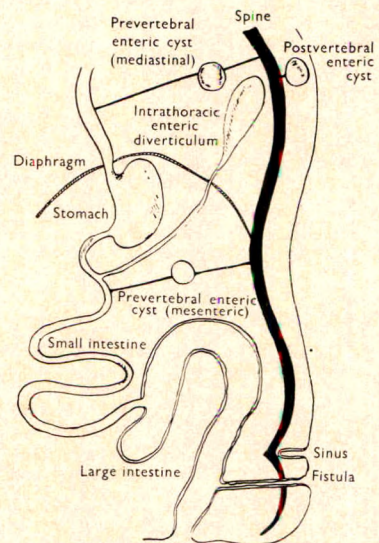


FIG. 9.—Distribution of developmental posterior enteric remnants.

(a) **Visceral Malformations.** The theoretical considerations accord well with the observed developmental anomalies classed in this paper as posterior enteric remnants. These may comprise certain mesenteric or posterior mediastinal 'duplications', diverticula or cysts connected by fibrous strands to the anterior aspect of the body of a vertebra situated cephalad to the enteric remnant. The vertebral body concerned is often bifid, and a complete anterior and posterior spina bifida occasionally exists.

Histological examination of the remnant will usually show the presence of smooth muscle and enteric mucosa in the walls of the lesion. The mucosal type may differ from that of the gut to which it lies adjacent, and it may be flattened and atrophic, the appearance giving no clue to its derivation. Occasionally broncho-pulmonary or other tissues primarily derived from the developing gut will be present.

The developmental posterior enteric remnants may be subdivided as follows:

(1) **FISTULAE.** When obliteration of the embryonic fistula fails completely the track passes back from the gut through the mesentery or mediastinum, traverses a complete spina bifida which may be coupled with a diastematomyelia or diplomyelia, to open on the skin in the midline of the back.

(2) **SINUSES.** The dorsal part of the embryonic fistula is all that persists. It forms a sinus derived from cutaneous or enteric tissues that passes forward from the midline of the skin of the back. There may be an underlying posterior or complete spina bifida.

(3) **POSTERIOR ENTERIC DIVERTICULA.** The ventral part of the embryonic fistula remains and communicates with the gut. There may be an associated anterior spina bifida or fibrous adhesion to a vertebral body.

(4) **POSTERIOR ENTERIC CYSTS.** Only an intermediate part of the embryonic fistula or diverticulum persists and the atrophic portions are represented by fibrous bands. These cysts may be prevertebral (posterior mediastinal or mesenteric), vertebral (spinal or mid-brain) or postvertebral in position. Many examples of the latter have been classed as teratomatous cysts. Anterior, combined or posterior spina bifida can be associated lesions.

Bremer (1952) proposed the term 'dorsal intestinal fistula' to cover this group of anomalies, a term we reject as so few of the lesions are true fistulae. The term 'enteric duplication' has also been applied to some of these lesions, causing confusion, as it should be restricted to anomalies attributable to defects of

embryonic vacuolation of the gut, an entirely different process (Bremer, 1944).

Malformations of the heart and great vessels, oesophageal atresia and hiatus hernia have also been observed in association with defective spinal development. Whilst their coincidence is compatible with the theory of the split notochord, positive evidence is lacking.

(b) **Spinal and Central Nervous Malformations.**

The gap in the dorsal tissue mass of the embryo, which is associated with a split notochord, may close without trace in the process of development. When this closure is less than complete the resultant spinal defect may range from a slight widening of the vertebrae to a complete anterior and posterior spina bifida. Minor degrees of anterior spina bifida produce the radiological appearance known as 'butterfly vertebrae', which may not be demonstrable without tomography. The more gross lesions may enclose enteric or cutaneous elements, as has been indicated. Pairs of hemivertebrae in these lesions may assume individual (if distorted) growth; fusion of the medial pedicles so formed results in the bony spur found with diastematomyelia (Fig. 10)

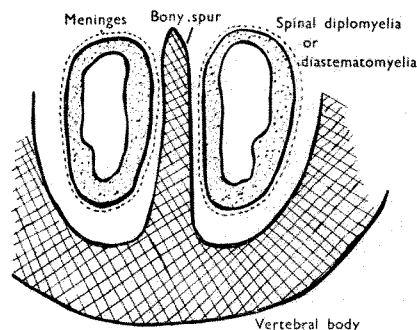


FIG. 10.—Diastematomyelia.

(Bremer, 1957). In this connexion it is noted that fusion of the cervical vertebrae constitutes the osseous element in the Klippel-Feil syndrome, and that these vertebral bodies are often split.

The spinal canal is widened in each of these types of vertebral modification, and anterior or posterior meningoceles may protrude where the spine is bifid. When the spinal cord itself is cleft, the separated halves seldom rejoin inferiorly, possibly due to tethering by the nerve roots. Each half of the cord is invested in meninges derived from the spreading mesenchyme, and the two median walls of the dura and arachnoid may fuse to form a sheet of tissue

which contains any remnant of an enteric fistula. Within the meninges each half of the neural groove develops, either as the lateral half of a spinal cord (diastematomyelia) or as one of a pair of whole but malformed cords (diplomyleia) (Herren and Edwards 1940). During late foetal life the spinal cord migrates up the spinal canal and the injured segment becomes separated from the bony lesion, a process which can be limited by the anchor of a long bony spur. Matson, Woods, Campbell and Ingraham (1950) describe the clinical picture and the relief of symptoms consequent on excision of the spur.

The visceral, cutaneous, spinal and nervous lesions described so far in relative isolation may coincide in a variety of combinations, while hamartomatous malformation of the affected tissues not infrequently contributes to their bizarre nature.

Clinical Reports

Various manifestations of the split notochord syndrome within the chest and abdomen have frequently been described in detail under a variety of titles. There are fewer records of posterior enteric remnants situated within or behind the vertebral column, and five of these cases are therefore described. Three are personal cases, and the others were recognized in the library of recent clinical photographs. The number in no way reflects the total experience of the condition at the Royal Hospital for Sick Children, Glasgow.

Case 1. M.F. This girl was seen by Mr. Matthew White at the age of 11 years when she began to get attacks of pain in the left thigh precipitated by coughing. She had a limp and the left lower limb was $\frac{1}{2}$ in. shorter than the right. A sinus 1 in. in diameter opened over the lumbo-sacral spine (Fig. 11); the surrounding tissues were tender but there was no neural deficit. Radiographs revealed a complete spina bifida of the lumbar spine and upper sacrum. A sinogram outlined the sinus to the laminae, and this part of the track was excised. The pathologist described it as a dermoid growth composed of skin elements and embryonic lung tissue. The lining was partly squamous epithelium in which were sebaceous glands and hair follicles. Adjacent were differentiated cartilage, embryonic bronchial cartilage and primitive lung tissues. The ciliated epithelium lining the bronchioles was supported by actively secreting mucous glands.

The sinus persisted but the girl remained well for four years, then being admitted to the Orthopaedic Unit, Western Infirmary (Mr. R. Barnes) with severe left sciatica of two weeks' duration. She was toxic and febrile to 102° F. with a fluctuant swelling above the sinus. She responded to treatment with sulphadiazine; penicillin and achromycin were ineffective.

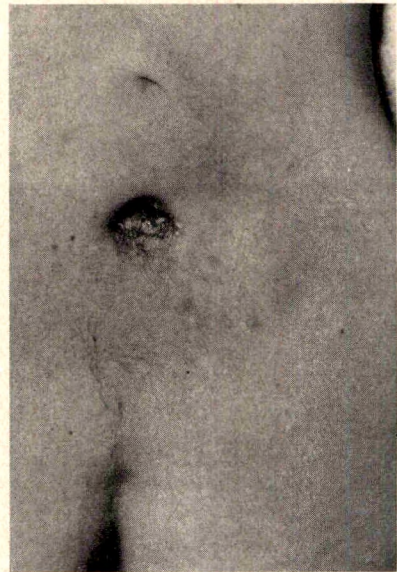


FIG. 11.—Case 1. Developmental posterior enteric sinus.

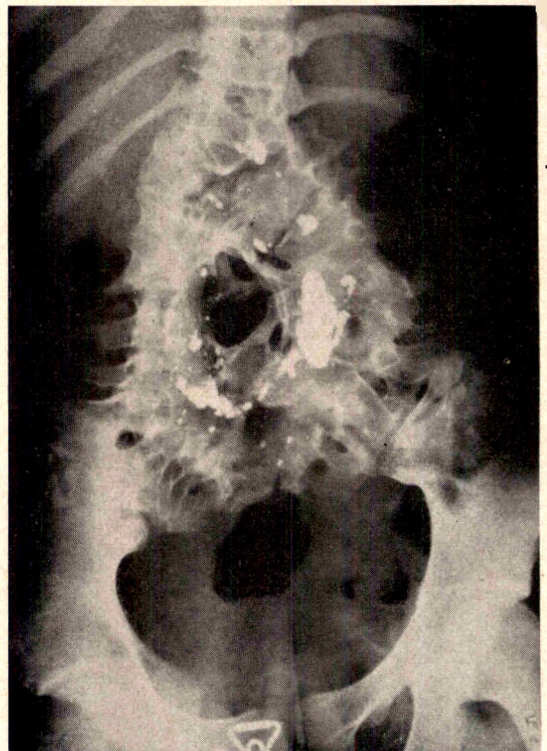


FIG. 12.—Case 1. Cysternal myelogram consistent with diastematomyelia.

Subsequent investigations included a cysternal myelogram. The contrast medium ran down to the lumbar lesion and outlined both sides of a solid swelling 'within the canal' (Fig. 12). Stereoscopic studies revealed a flake of bone consistent with diastematomyelia in the upper lumbar spine. The cerebrospinal fluid was normal (Lange negative, protein 30 mg. %, sugar 50 mg. %, chlorides 714 mg. %).

After three and a half months' bed rest the child was discharged symptom free, only to be readmitted 10 months later for a further two months because of recurrent left sciatica. She was again pyrexial and toxic with a diffuse, tender, non-fluctuant swelling of the left thigh and buttock extending to the lumbo-sacral area. The leucocyte count was 25,000 c.mm., the urine was normal and a blood culture proved sterile. The left femoral radiograph was normal. Urgent exploration of the left thigh opened an abscess deep to the tensor fasciae latae, yielding two and a half pints of pus from which coliform organisms were cultured.

She received tetracycline and responded well, but sinuses intermittently discharged from the left thigh and lumbo-sacral skin. This persisted for 10 months after she left hospital and she was therefore readmitted. Secondary infection with penicillin-sensitive *Staphylococcus aureus* had now occurred, the sinuses following the course of the previous abscess cavity. Healing was not promoted by systemic penicillin, so local instillation of chloramphenicol was tried. After treatment for one month an abscess reformed from the spinal defect and again *Escherichia coli* was isolated from the pus. Further drainage and chloramphenicol instillations sterilized the cavity, leaving a chronic sinus. After eight months in hospital, treatment was continued in the out-patient department and healing has slowly occurred.

Case 2. O.C. This girl was admitted under the care of Mr. Andrew Laird four days after premature birth with a gross malformation of the back. Bowel herniated extensively through the centre of the lumbo-sacral region forming a 'prolapsed natural colostomy' with exposed intestinal mucosa. The stoma was at the lower part of the prolapse and through it a catheter was passed into a prolapsed rectum (Fig. 13). Radiographs of the spine show duplication below the second lumbar vertebra and prolapse of gut backwards through the spinal defect (Figs. 14 and 15). Active treatment was not attempted and the infant died at home after eight days in hospital.

Case 3. F.McL. This boy was admitted to Mr. Dennison's wards at the age of 4 weeks. A hemispherical swelling 1 in. in diameter protruded in the midline over the upper sacrum. The basal two-thirds of the swelling were covered by normal skin and the apical third with mucous membrane which showed intermittent waves of peristalsis. In the centre mucus exuded from the orifice of a sinus (Fig. 16). This 7 lb. 6 oz. infant appeared normal in all other respects, including radiographs of the spine and barium studies of the gut, apart from a skin dimple below the lesion.

The lesion was excised together with the skin dimple, to which a narrow fibrous pedicle arose from the sacral hiatus. Healing was uncomplicated.

The excised ellipse of skin measured 3 × 2.5 cm. and its centre looked like an enterostomy stoma from which a sinus penetrated just short of the deep surface of the specimen. Microscopy showed the skin to become continuous with a blind pouch of small intestine complete in all its layers. There was no evidence of meningo-coele (Fig. 17).

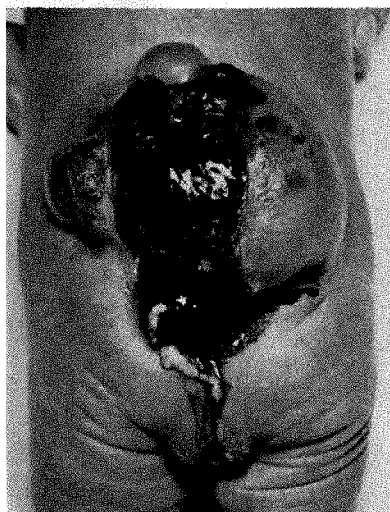


FIG. 13



FIG. 14



FIG. 15

FIGS. 13 to 15.—Case 2. Developmental posterior enteric fistula. Radiographs of spine. Complete spina bifida.

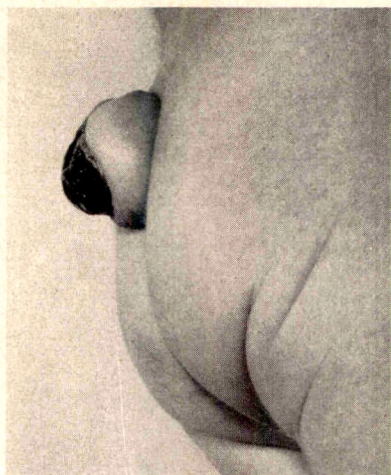


FIG. 16.—Case 3. Developmental posterior enteric sinus.



FIG. 17.—Case 3. Microscopic appearance of excised sinus.

Case 4. A.G. This 6 lb. 1 oz. girl was admitted to Mr. Dennison's wards within 24 hours of her birth at term. Her general health was good, but a meningocele 3.5 cm. in diameter covered by thin intact skin arose from the lower thoracic spine. Beneath the sac was an umbilicated red area 1 cm. in diameter, which had a

smooth moist surface changing abruptly to normal skin at the periphery. The umbilication twitched slightly coincident with inspiration, and a probe was passed to 7 mm. An ill-defined soft swelling 2.5 cm. in diameter, covered by normal skin and with a bony spur palpable in its depths, extended on each side of the red area from below (Fig. 18a). A lower dorsal combined spina bifida was shown radiographically (Fig. 18b).

On the third day the meningocele was excised with ligation of a narrow pedicle. The umbilicated lesion was found to be flanked by loose fatty tissue resembling infantile omentum but containing some muscle. The inspiratory retraction of the red dimple ceased when it was isolated to its pedicle, which emerged from an orifice, incomplete above, in the apex of a cone of fused spinous processes. The lesion was excised without removal of bone or exposure of the spinal cord. The child was discharged well and healed on the twenty-fifth post-operative day.

Microscopy confirmed the absence of nerve tissue in the meningocele. The umbilicated area was covered by poor squamous epithelium, ulcerated in places. The track penetrating the deeper tissues was lined partly by squamous and partly by respiratory epithelium, and mucous glands were present in the wall. No smooth muscle was seen, but striated muscle and cartilage were in close proximity. The skin around the lesion showed an excess of the normal appendages in the dermis (Fig. 19).

Case 5. M.G. This 8½ lb. boy was admitted 24 hours after a normal birth at term. In addition to exstrophy of the bladder he had intestinal obstruction due to anal agenesis. His rudimentary scrotum was bifid and the testes were undescended. The two halves of the pelvis were separated not only anteriorly but also posteriorly where the sacrum was bifid. Projecting backwards from the apex of the sacral cleft was a bony spur entering a globular mass of tissue covered by skin bearing small flat haemangiomatous areas. A bulging smooth red membrane occupied the lower part of the cleft, and a small meningocele arose from above the bony spur. Limited active movement was seen in the lower limbs (Fig. 20).

Treatment was limited to excision of the meningocele with the bony spur and tissue mass, and left iliac colostomy under local anaesthesia. Chromosomal sexing was established from buccal smears. Although the child appeared to thrive he died suddenly and unexpectedly on the tenth day.

No specific cause of death was apparent at autopsy, which demonstrated the additional presence of a mild hydrocephalus without Arnold-Chiari malformation. The rectum was found to be a blind pouch passing back between the ureters to form the bulging membrane that occupied the lower part of the sacral cleft, and this membrane was covered on both its surfaces with intestinal mucosa (Fig. 21). The tissue mass excised at operation proved to be a teratomatous dermoid containing a developing tooth.



FIG. 18a.—Case 4. Developmental posterior enteric sinus.

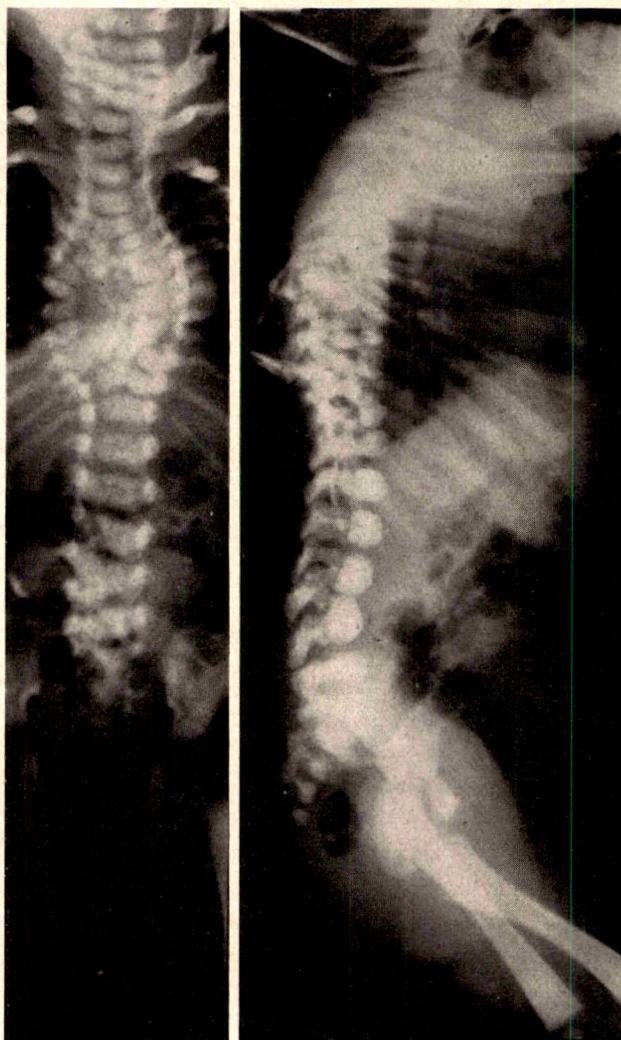


FIG. 18b.—Case 4. Radiographs of spine.

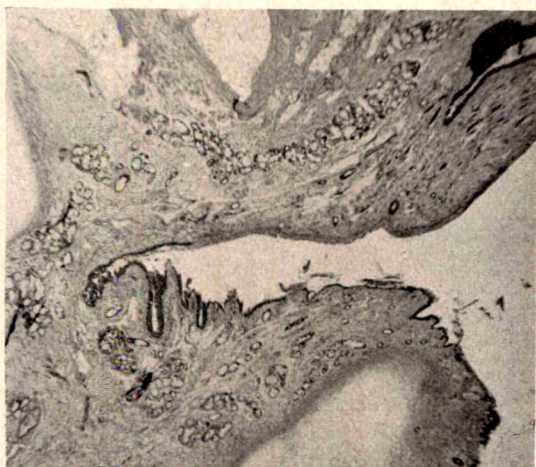


FIG. 19.—Case 4. Microscopic appearance of excised sinus.

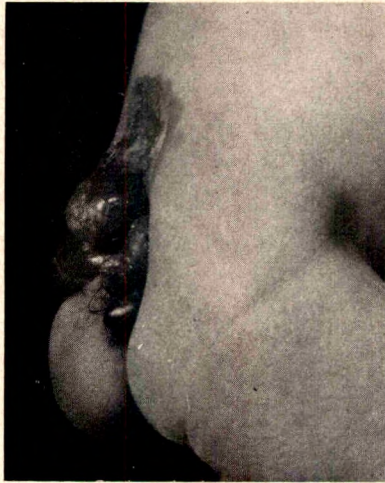


FIG. 20.—Case 5. Developmental posterior enteric sinus with meningocoele, dorsal teratomatous dermoid and exstrophy of bladder (vesico-intestinal fissure).



FIG. 21.—Case 5. Microscopic appearance of membrane lying in sacral cleft.

Case Commentary

The first patient is exceptional in having reached the age of 18 years in relatively good general health. In addition to her combined anterior and posterior spina bifida, diastematomyelia with a bony spur and splitting of the meninges investing the spinal cord have been demonstrated. The pulmonary tissues in the excised sinus have shown potentialities comparable with the foetal fore gut, whilst the repeated coliform infections which followed the partial excision raise the possibility of a tiny fistulous connexion with the gut. The second patient is an uncommonly gross example of a fistula from the hind gut. Peristaltic activity in the third case is remarkable, the enteric sinus lacking any residual connexion with the gut. The fourth case may be contrasted; here muscle contraction coincided with inspiration, suggesting that an abnormal branch from a phrenic nerve activated the striated muscle in a remnant which remotely caricatured bronchial elements. The fifth patient has a form of vesico-intestinal fissure (Hall, McCandless and Rickham, 1953) showing a dorsal teratomatous dermoid in association with posterior enteric diverticulum. The existence of intestinal mucosa on both surfaces of the terminal membrane of the diverticulum is consistent with it having been formed by the process of pinching off an embryonic fistula. The defects in the perineum and lower abdominal wall are consistent with a linear midline cleft of the caudal end of the embryo and modern concepts of the aetiology of exstrophy of the bladder (Glenister, 1958).

Discussion

The researches of Lereboullet (1863) on the effects of artificial insemination on the ova of the pike showed some of the resultant embryos to be split sagittally between a normal head and tail, the yolk sac being exposed centrally in the dorsal gap. By destruction of the first daughter cell of the frog ovum Roux (1888) produced embryos which were split but incomplete, but it was Hertwig (1892) who showed the production of true 'ring embryos' in the frog by fertilization of post-mature ova; he accepted the dorsal clefts as a variation of the neurenteric canal or blastopore, appreciated their role in the production of combined spina bifida, and coined the word diastematomyelia. Similar changes have been produced in mammalian embryos (Warkanay, 1960).

Oehlecker (1909) emphasized that the commoner variety of posterior spina bifida is the result of a separate and distinct anomaly occurring much later in foetal life, but where there has been a complete spina bifida anterior fusion and repair leaves a

persisting posterior defect. With both varieties of spina bifida there may be hamartomatous changes in the overlying tissues, often classified as teratomata (Nicholson, 1937).

Switzer (1839) claims the first clinical description of combined spina bifida, the anterior cleft of which was traversed by coils of gut, and Muscatello (1894) reviewed a number of comparable cases. Lucksch (1903) described a still-born infant with an intestinal fistula traversing an upper dorsal spinal defect, and Keen and Coplin (1906) reported a patient with a congenital rectal fistula of bronchial structure that passed through the sacrum and cauda equina to open on the skin of the back. The Committee on Spina Bifida, Clinical Society of London, in their Report (1885), recognized that duplication of the centre of vertebral bodies could be associated with bony spurs dividing the spinal cord.

The modern concepts which link the observations on animal embryos with the clinical findings in man have been developed mainly by Saunders (1943), who more recently extended his theory jointly with McLetchie, Purves and Saunders (1954). Very similar conclusions were reached independently by Bremer (1952) and the introductory outline of this paper is based on the work of these authors.

Hertwig's theory that complete vertebral clefts are due to arrest of the normal fusion of the blastopore lips laid the foundations of discussion. The views of Budde (1912, 1926), Adelman (1920), Gruber (1923, 1926) and Bell (1923) included speculation on the applicability of this theory to mammals. Gruber (1926) estimated the time of development of the anomaly and the role of mechanical compression, and Budde (1926) suggested that persistence of the primitive streak could provide an abnormal ento-ectodermal connexion.

Discounting Hertwig's theory, Feller and Sternberg (1929) suggested that a cell rest from the primitive knot (Hensen's node) persists and causes a cleft notochord; Korff (1937) further postulated proliferation of the cell rest to form an abnormal organ. These workers were the first to draw attention to the importance of the cleft notochord, an anomaly seen in human embryos by Johnston (1931) and Frazer (1931). The migration of the primitive knot with growth discounts the possibility of its derivatives splitting the notochord. The knot lies in the blastopore lip of the normal neurenteric canal, a minute tube which exists for a brief period connecting yolk sac and amniotic cavity; subsequent embryonic growth and development are such that the remains lie finally at the tip of the coccyx, caudal to any spinal lesion. For this reason Bremer (*loc. cit.*) avers that the lesion in the 'ring embryo' is an

'accessory neurenteric canal' and a perversion rather than an arrest of normal development.

An alternative theory proposed by Fallon, Gordon and Lendrum (1954) postulates an upset in the normal process of exhalation of the notochord, which occurs in the third week of foetal life (Keith, 1948). They were influenced by the work of Stoeckel (1935) and Veeneklaas (1952), who noted the intimate contact of the endoderm with the notochord in early foetal life, and by the description by Patten (1946) of a 6-mm. human embryo with local kinking and fusion of the notochord to the neural tube. One of the authors has since abandoned this conception of the embryology in favour of that of Saunders (Lendrum, 1958).

Saunders (*loc. cit.*) has emphasized that anterior or combined spina bifida most frequently involves the cervical and cervico-dorsal vertebrae and many affected infants are still-born with skull defects or anencephaly; stomodeal duplication occurs occasionally (Morton, 1957). As the cephalic end of the notochord develops first this is in accordance with the theory of Stockard (1921) that an organ is most sensitive to disturbances in development at its moment of inception.

Summary

Evidence is presented that an abnormal splitting of the notochord, known to occur in the developing embryo, can cause a wide variety of malformations. These may involve the viscera of the chest or abdomen and incorporate abnormal tissue remnants of enteric derivation; they include combined spina bifida and allied vertebral malformations, together with associated central nervous anomalies and defects in the development of the skin and subcutaneous tissues of the back.

Hitherto these malformations have been individually named; it is now suggested that they can be usefully classified together as manifestations of the 'split notochord syndrome'. Their apparent rarity has been due to failure to appreciate the common basic aetiology.

A terminology is suggested for the abnormal structures of enteric origin in this group. They are classed as developmental posterior enteric remnants, be they fistulae, sinuses, diverticula or cysts.

Five illustrative cases displaying these enteric remnants are described.

Our thanks are due to Mr. Matthew White, Mr. A. P. Laird, Mr. W. M. Dennison and Mr. T. B. Gardiner for their help with clinical details of their patients. We are most grateful to Dr. Norma Macfarlane who prepared the line drawings and to Mr. J. A. L. Evatt, Mr. J. R. Devlin and Mr. W. B. Mason for their photography.

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ACCESSORY ENTERIC FORMATIONS

A CLASSIFICATION AND NOMENCLATURE

BY

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There is considerable confusion in the present classification and nomenclature of accessory enteric formations—enterogenous cyst, archenteric cyst, gastro-thoracic cyst, duplication, etc. The purpose of this paper is to present a practical classification founded on the basic embryological deviations and a systematic nomenclature. Many of the anomalies are of some rarity and few surgeons are likely to acquire a series of any great size. The frequency of diagnosis should increase with an awareness of the types and the use of a common terminology.

The proposed classification is:

1. Duplications
2. Vitelline remnants
3. Dorsal enteric remnants

All have a typical enteric structure of smooth muscle and epithelial lining, not necessarily that of gut, to which it lies adjacent or from which it originates. In the third group the structure may be not of gut but of a gut derivative.

Classification

1. Duplications. This term should be restricted to these formations, either tubular or spherical, which lie in contiguity with normal bowel and which share with it a common blood supply and usually a common muscle coat. There may or may not be communication between the normal and anomalous lumina, and the dividing septum may be muscular or merely a double layer of epithelium.

During early foetal life, embryo and gut grow at a similar rate, a rate which soon becomes inadequate for the latter if the necessary absorptive area is to be provided. Accordingly, the rate of growth of the gut accelerates with thickening of the epithelial lining and obliteration of the lumen and subsequent recanalization by the coalescence of vacuoles which appear within the epithelium (Johnson, 1910). Coalescence of an additional group of vacuoles, which fail to rupture into the normal lumen, causes the formation of duplications, spherical or tubular, depending on the length of bowel affected.

2. Vitelline Remnants. Remnants of vitello-intestinal origin are included in the classification because firstly they are accessory enteric formations, secondly there are aetiological similarities to dorsal fistula, and thirdly there is a similarity in the two groups of remnants found after birth. There is little justification other than usage for perpetuating the present names of Meckel's diverticulum, enterocystoma, enteroteratoma, raspberry tumour, etc.

Such remnants represent failure of closure of the vitello-intestinal duct. The mid-gut is in free communication with the definitive yolk-sac until the late pre-somite stage when the communication narrows to form the vitello-intestinal duct which in turn disappears by the end of the sixth week of foetal life. Incomplete obliteration gives rise to the anomalies shown in Fig. 1, which I suggest be called vitelline fistula, sinus, cyst and diverticulum. Similarly, I propose that an obliterated vitelline artery be called a vitelline cord.

3. Dorsal Fistula Remnants. During the second half of the nineteenth century, it was shown experimentally that sagittal clefts could be produced in frog and pike embryos with dorsal protrusion of the yolk-sac (Lereboullet, 1863; Roux, 1888; Hertwig, 1892). Bremer (1952) has suggested a similar occurrence during early human development with rupture of the yolk-sac herniation and formation of a fistula between yolk-sac and amniotic cavities, while Saunders (1943) and McLetchie, Purves and Saunders (1954) have postulated that a cleft notochord leads to adhesion of yolk-sac endoderm to ectoderm with subsequent erosion and fistula formation. However, during that phase of normal development when the notochord becomes intercalated in yolk-sac endoderm, openings appear in the floor of the notochord canal, thus establishing temporary communication between yolk-sac and amniotic cavities. Whatever the precise mechanism, it must be assumed that at some phase of pre-somite development such a fistula occurs. The development and obliteration of the vitello-intestinal duct is

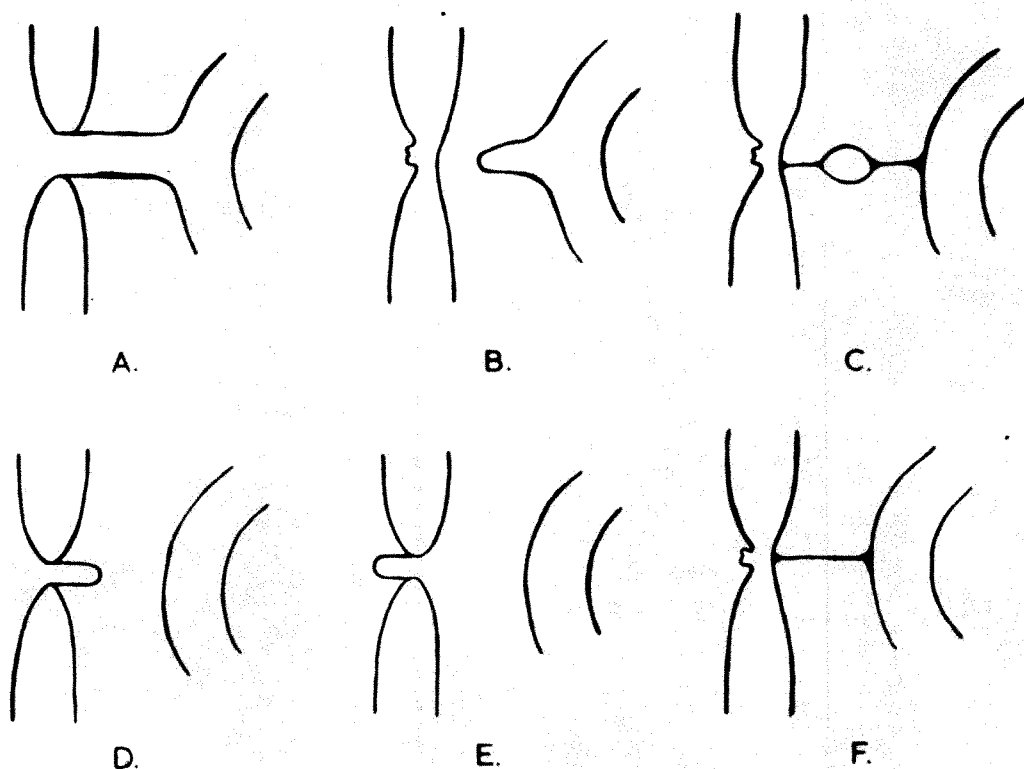


FIG. 1.—A. Vitelline fistula; B. vitelline diverticulum; C. vitelline cyst; D. vitelline sinus; E. prolapsed vitelline sinus; F. vitelline cord.

TABLE I
PRESENT AND REVISED NOMENCLATURE

Group	Present Nomenclature	Revised Nomenclature
Duplication	Duplication Ileum duplex Enterogenous cyst, etc.	Duplication: Tubular Spherical
Vitelline remnants	1. Patent vitello-intestinal duct Umbilical fistula 2. Enteroteratoma Umbilical polyp Etc. 3. Enterocystoma 4. Meckel's diverticulum 5. Omphalo-mesenteric cord	1. Vitelline fistula 2. Vitelline sinus 3. Vitelline cyst 4. Vitelline diverticulum 5. Vitelline cord
Dorsal enteric remnants	1. Accessory neurenteric canal 2. 3. Mediastinal enterocystoma Gastric thoracic cyst Archerteric cyst Etc. 4. Giant diverticulum Macrodiverticulum Congenital diverticulum	1. Congenital dorsal enteric fistula 2. Congenital dorsal enteric sinus 3. Congenital dorsal enteric cyst (a) Prevertebral (b) Postvertebral (c) Intraspinal 4. Congenital dorsal enteric diverticulum

part of normal human development, and, since it traverses a cavity, its obliteration is an isolated process. The occurrence of a dorsal enteric fistula is abnormal, hence less common, and, since it traverses spine to reach the dorsal surface, not only has the fistula to be obliterated but the vertebral and neural defects have to be repaired. The various enteric, neural, and vertebral defects persisting after birth represent the varying degrees of success attained. Elongation of the gut during foetal life leads to wide separation of the original spinal and enteric regions, hence the association of cervical and thoracic spinal anomalies with caudad enteric lesions.

Analogous with vitello-intestinal remnants one may find (Fig. 2):

(1) Congenital dorsal enteric fistula when the whole tract persists and presents as a fistula passing from gut through spine and cord to open on the midline posteriorly.

(2) Congenital dorsal enteric sinus when only the posterior part persists.

(3) Congenital dorsal enteric cyst when an inter-

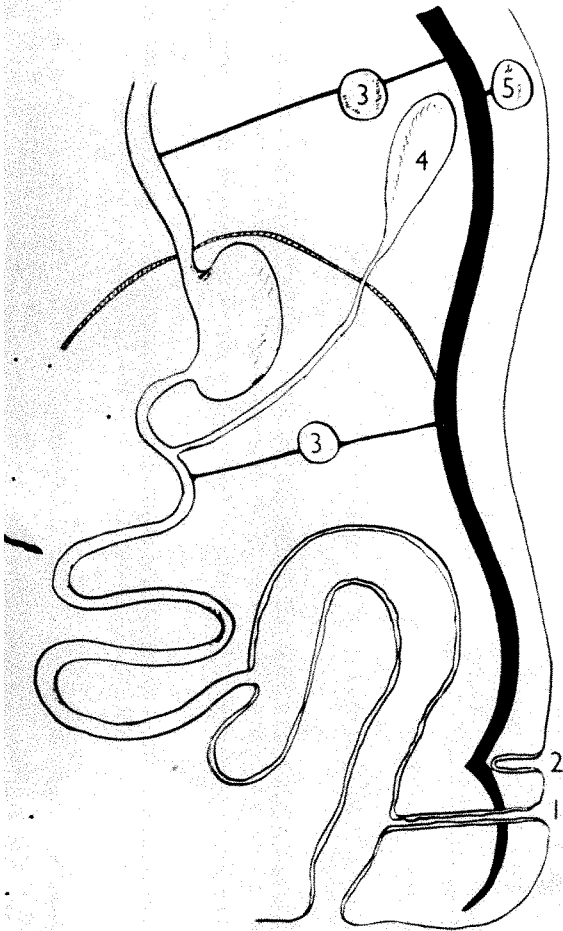


FIG. 2.—1. Dorsal enteric fistula; 2. Dorsal enteric sinus; 3. Dorsal enteric cyst; 4. Dorsal enteric diverticulum; 5. Dorsal enteric cyst.

mediate part persists. The cyst may be pre- or post-vertebral or intraspinal in position, and may have fibrous attachments to gut or spine.

(4) Congenital dorsal enteric diverticulum when only the anterior part persists and connexion with the lumen of the gut is maintained.

There may be varying degrees of concomitant vertebral abnormality with diastematomyelia or diplomyelia. This aspect is discussed more fully in another communication (Bentley and Smith, 1960).

Summary

A classification and nomenclature of accessory enteric formations is proposed which should end the present confusion and facilitate the recognition of the less common types.

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TOTAL COLECTOMY AND ILEO-ANAL ANASTOMOSIS IN THE TREATMENT OF ULCERATIVE COLITIS IN CHILDREN*

BY

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Modern trends in the treatment of ulcerative colitis are pointing towards earlier and more radical surgery. Ileostomy is no longer found adequate, simultaneous ileostomy and subtotal or total colectomy being the method preferred by most experienced surgeons.

In childhood the disease is relatively rare; in a large series only about one-tenth of all the cases occurred in children (Bargen and Kennedy, 1955). It is, however, apt to take a more serious course. The mortality after medical treatment is high. In a large Swedish series it was 12% (Lagercrantz, 1955). According to the same series, the chronic, intermittent is the most common type, comprising 79% of all cases. The disease results in gross delay of growth and maturity and because of long periods of hospitalization the children are unable to follow their normal school education. Cancer is a rare complication in childhood, but cases starting in childhood and persisting 10-20 years are more liable to malignancy than those starting in adulthood. According to Rosenquist, Öhrling, Lagercrantz and Edling (1959), 17 of 26 cases of cancer developed in ulcerative colitis were taken ill with their primary disease before the age of 15, and cancer may appear even after years of apparent cure. Consequently it must be of current interest to discuss the advisability of early and radical surgical treatment of ulcerative colitis in childhood also.

At the University Clinic of Paediatrics in Copenhagen we have during the last two years performed four colectomies for ulcerative colitis in children, two cases being of the chronic intermittent type and two of the acute, fulminating type. Our first case was interesting in more than one sense.

The patient, a 13-year-old girl, developed ulcerative colitis at the age of 2 years. She had been hospitalized several times during infancy, and was treated medically according to the current methods until the age of 11

when an ileostomy was performed. This operation had a very good effect upon her general condition although the inflammatory changes persisted. One and a half years later a subtotal colectomy was performed. The colon was grossly inflamed with large ulcerations and pseudopolyposis and in two different areas in the transverse colon cancer had developed (Fig. 1). The



FIG. 1.

rectum was not removed. The operation was thought to be radical and the post-operative course was smooth.

Two months afterwards an ileo-rectal end-to-side anastomosis was done. On this occasion no signs of recurrence of the cancer were found, but three months

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

later she was readmitted acutely ill with symptoms of ileus. At laparotomy it was found that she had a diffuse peritoneal carcinosis. Of course nothing could be done and the child succumbed to her disease in a month. At autopsy it was found that a severe ulcerative proctitis had recurred.

From this case we learned firstly that cancer may very well develop in spite of an ileostomy, showing the importance of a total or subtotal colectomy, once surgical treatment has been decided upon. Secondly we learned that ileo-rectal anastomosis is not the ideal procedure since it may be followed by recurrence of a haemorrhagic proctitis.

Ileo-rectal anastomosis has been advocated for selected cases by several authors (Corbett, 1958; and Aylett, 1957, in England) and has also been used in children (Ehrenpreis, 1959). We feel, however, that owing to the risk of relapse of ulcerative proctitis in the remaining part of the rectum and also to the risk of cancer, total colectomy must be the preferred procedure. Since a permanent ileostomy, even with modern equipment, is very incapacitating, especially in a child or a young person, we decided to attempt an ileo-anal anastomosis.

Up till now we have done this operation in two cases. They have both been operated on in two stages, the first stage being ileostomy and subtotal colectomy. Six months later we anastomosed the ileum to the anus and removed the rectum using the pull-through technique described by Swenson (1958) for Hirschsprung's disease. We have found it important to postpone the second stage at least six months. In the intervening period the general health can be re-established and the blood chemistry, which may be difficult to keep within normal ranges during the first period after ileostomy, can be regulated. Also in the span of six months the stools will become semi-solid, owing to an increasing absorption of liquid from the terminal ileum, and are thus less irritating.

From a technical point of view the second stage has been easy, the only difficulty being the isolation of the rectum down to the anus. Because of inflammation it was in both cases very adherent to the surrounding structures. The removed rectum was in both cases grossly inflamed except for the most distal part.

Our first patient thus treated was a 13-year-old girl. Her illness started at the age of 5 years and was of the chronic, intermittent type. The final operation, an ileo-anal anastomosis, was performed a year ago. She is now in excellent health. She has four to five bowel movements during the day, the stools being semi-solid and not irritating, and she is completely continent and undisturbed during her sleep. She now attends school without absence.

Our second case was a 7-year-old boy with an acute fulminating ulcerative colitis. The ileo-anal anastomosis was performed a couple of months ago. With the exception of some incontinence his convalescence was uneventful. On discharge, which took place only recently, he was in excellent health with a promising weight curve.

A third case, a 13-year-old boy, also suffered from the acute fulminating type and had a colectomy six months ago (Fig. 2). He still has his ileostomy and is in very good



Fig. 2.

condition. It is our intention to perform an ileo-anal anastomosis this autumn.

Summary

In children ulcerative colitis is apt to take a rather fulminant course. Medical treatment is tedious and takes a very long time. In our experience children will stand a radical colectomy and ileostomy very well and will develop in a natural way afterwards. It has, however, been our aim to avoid an incapacitating permanent ileostomy. An ileo-anal anastomosis, using the same technique as in Swenson's pull-through operation for Hirschsprung's disease, has up till now been used in two cases and seems to be a promising solution.

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SURGICAL ASPECTS OF PATENT DUCTUS ARTERIOSUS*

A REVIEW OF 228 CASES

BY

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Three years ago Hay and Ward (1956) reviewed the results of surgery for 108 cases of patent ductus arteriosus treated at the Royal Liverpool Children's Hospital. The object of this communication is to review the present position at the same hospital from the purely surgical point of view. A further 120 cases have received surgical treatment up to December 31, 1958, making a total of 228 cases available for review, with a minimum follow-up period of five months.

Surgery of patent ductus arteriosus comes of age this year as on August 26, 1938, Gross performed the first ligation operation (Gross and Hubbard, 1939). But the literature on the surgery of patent ductus arteriosus is not very large, considering that the abnormality is such a common one. In fact the contributions of Gross and Hubbard (1939) and Gross (1952) mark the only real major landmarks in the surgery of the condition, reporting the technique of simple ligation and of division respectively. In this second paper Gross reports the extraordinary number of 482 divisions of the patent ductus with 10 deaths. Shapiro and Johnson (1947), reporting 626 operations for patent ductus performed by 48 surgeons, record a mortality of 4.9% and a recanalization figure of 8.7%. They report 172 divisions of their own with no fatality and no recanalization. They state categorically that the operation of ligation is obsolete and should only be done when division is impracticable. Yet even now many surgeons, the present writer among them, have felt a natural hesitancy in substituting the technically more difficult procedure of division for the rather easy one of ligation.

Since Hay and Ward's first report, two other large series of operations for patent ductus arteriosus have appeared in the English literature. Nicks and Molloy (1956) describe a series of 155 cases from New Zealand with 138 operations. In all but five

cases the surgical method used was double ligation with silk, and there were only three recurrences in the 80 cases which had adequate follow-up details. The overall mortality was 2%. Mozen (1957) reviewed 143 cases operated on in Dr. Claude S. Beck's clinic in Cleveland, Ohio. The overall mortality was 2.14%. The surgical method used for closure was ligation and suture in 53 cases, division in 88 and exploration alone in two. Only one example of recanalization is mentioned as having taken place in the whole series, though follow-up details may be incomplete.

The fact that division may be proved statistically to be safe should not be allowed to obscure the fact that the division of a large blood vessel must carry with it an appreciable risk from accident. Nor can it be said categorically at the present time that a suture line in such a major vessel as the aorta or the left pulmonary artery is free from the risk of development of a weakness at some future date. Nevertheless the review made by Hay and Ward (1956) shows that the results of the simple ligation operations are far from perfect. Although there was only one death in 108 cases (a case in which the ductus was not tied because a reversed shunt was found) there was in fact failure to secure closure of the ductus in 10 cases, while a further four showed evidence of recanalization during a period of observation varying from one to 12 months. In addition, operation was abandoned on one occasion because friability of the ductus led to difficulty in dissection and to haemorrhage, which was controlled only with difficulty. Even if the case with the reversed shunt is excluded, together with two of the early recanalizations which appeared to close spontaneously, we are left with the uncomfortable fact that the object of the surgical procedure was not completely successful in 13 of the 107 'eligible' cases (a failure rate of 12%). Here one must say that there was evidence of reduction of the shunt in all these cases. The 'gross' failure rate for all cases was 14% (16 in 108 cases). In the ensuing discussion this series of cases

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

will be referred to as Series 1, the newly reported group as Series 2.

The Technical Problem

When the causes of failure to close the ductus were considered, it immediately became apparent, as Hay and Ward pointed out, that there was a close relationship between the success of the operation, then performed entirely by the method of double ligature, and the diameter of the ductus. In 53 cases in which the diameter was 7 mm. or less there was not a single recanalization, whereas this process was observed in no fewer than 16 of the 55 cases in which the ductus had a diameter of 8 mm. or more. In fact only eight of the 20 cases in which the diameter was in excess of 10 mm. were permanently closed by ligature (Table 1).

TABLE 1
EFFICIENCY OF CLOSURE RELATED TO SIZE OF DUCTUS

	Diameter of Ductus (mm.)				Total
	Less than 5	5-7	8-10	More than 10	
Series 1	4 (—)	49*(—)	35 (4)	20†(12)	108 (16)
Series 2	3 (—)	66*(1)	39 (2)	12 (2)	120 (5)
Total	7 (—)	115 (1)	74 (6)	32 (14)	228 (21)

Figures in brackets indicate number of failures

* Includes two cases of 'small' ductus, size not recorded

† Includes five cases of 'wide' ductus, size not recorded

While the magnitude of the failure rate with larger ductuses was not at once appreciated by us, it had for a long time been obvious that the very large ductus was not technically suitable for ligation. One reason for this is that the large ductus usually has a large flow through it with a raised pressure in the pulmonary artery. The very large ductus, in which the diameter is greatly in excess of its length, with its sclerotic walls, presents a formidable surgical problem.

This was at first tackled by attempting ligation by linen thread over a small pad of gauze or lint. This often seemed to result in obliteration of the lumen at the time of operation, but in only one instance (a 14 mm. ductus) was the closure permanent. Next the effect was tried of tying ligatures while the blood pressure was temporarily lowered by the ganglion-blocking agent Arfonad. This again seemed usually to provide satisfactory immediate closure, but the end results were equally disappointing.

With this unsatisfactory situation in mind the methods of closing the ductus were reviewed. First of all a point of anatomy was made which is not

always appreciated. The ductus in the unborn child is virtually a continuation of the pulmonary artery, and has an oblique entry into the aorta which is in most instances maintained even after the pulmonary circulation has been opened up by the establishment of breathing. When the ductus fails to close and the left to right shunt becomes established, the blood has to take a very sharp turn back into the pulmonary artery from the aorta (Fig. 1a). This no doubt

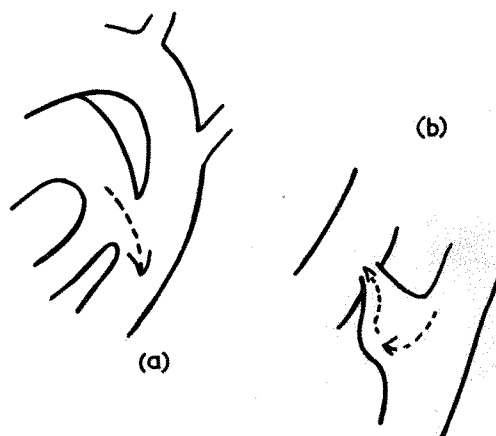


FIG. 1.—Evolution of patent ductus arteriosus (a) in foetal life; (b) in extra-uterine life.

accounts for the observation frequently made at operation, that the thrill is usually much more obvious in the main trunk of the pulmonary artery than in the left branch. But, in addition, there is a point of impact of the stream on the area of the aortic wall immediately adjacent to the origin of the ductus, but on the distal (caudal) side of the actual orifice. Much as a river erodes its banks on the convexity of a curve, so must this stream of blood, which is often nearly reversed in direction, exert a continual pressure on this area. The common shape of the ductus is conical, with a much wider opening into the aorta than into the pulmonary artery (Fig. 1b). The aorta itself is frequently appreciably wider just below the ductus than above it for the same reason. The ductus has often been described as spindle-shaped or cylindrical, but in the author's experience this is only exceptionally the case. The short, wide, 'high-pressure' ductus may be virtually cylindrical if it can be said to have any length at all, but the average ductus only assumes a spindle shape if traction on it pulls out some of the wall of the pulmonary artery. Firm pressure just in the angle between the aorta and ductus will restore the apparent cylindricity of the

vessel, and indeed a ligature may be tied here without much difficulty. Such a ligature tends, however, to be obliquely placed and is as insecure as if an attempt were made to close a hole in the side of the aorta by ligation (Fig. 2). It is naturally

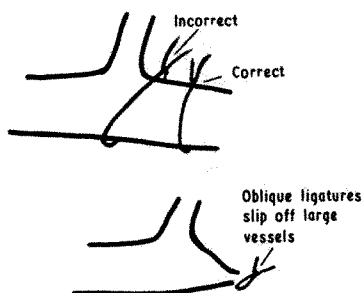


FIG. 2.—Correct and incorrect ligatures.

pushed towards the narrowest part of the ductus and then will not fully occlude the lumen of the vessel. The truly effective position for an occluding ligature is at the narrowest point of the ductus, and perhaps a single ligature properly placed there will suffice to obliterate the vessel. Many surgeons recommend multiple ligatures on the ductus; yet if further ligatures are to be tied after the ductus has been ligated at each end, there is a real danger of causing a rupture of the ductus, with catastrophic haemorrhage as a result.

Blalock (1946) met this difficulty by applying an encircling suture at each end of the ductus, transfixing the ductus in the middle and tying another ligature over it. Such an encircling suture at the aortic end would tend to come under excessive tension and might not be truly effective in maintaining permanent closure. A simpler method, which has been used more recently in our cases, is to ligate the ductus near the aortic end and then to close the lumen by a multiple transfixion suture of 3/0 arterial silk placed at the narrowest portion of the ductus (Fig. 3). A second ligature, which was passed but not tied before applying the stitch, is then tied over the narrowest portion of the ductus, that is, near the pulmonary end.

It is probably important to use correct ligature material but there is some difference of opinion among surgeons as to which is best for the purpose. We had formerly used a rather fine (No. 35 or 40) linen thread but latterly changed to the stronger No. 25 thread and feel that this is more satisfactory. Linen thread is stronger than silk and holds a knot very securely: it seems likely that a very thick strong ligature, e.g. the 'umbilical tape' of American

authors, will give a less satisfactory closure than a medium sized thread.

Finally, division of the ductus has been undertaken in cases when it is large or unusually thick-walled. The method we favour is one learned from Professor

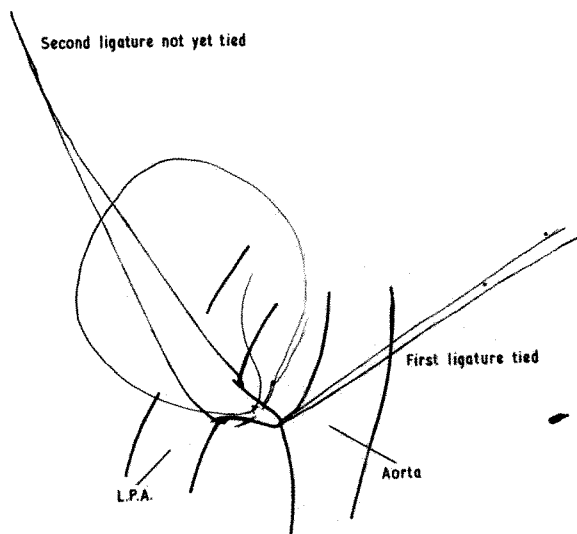


FIG. 3.—Ligatures and transfixion suture of patent ductus arteriosus.

A. G. Brom of Leiden, in which Potts' aortic clamps are applied from the lateral aspect of the ductus, which gives more room than if they are placed in the long axis of the descending aorta. The vessel may be progressively divided and sutured, usually without undue difficulty. Clamps similar to Potts' aortic clamps but bent at a right-angle (designed by Miss I. Forshall for neonatal oesophageal surgery)* are very satisfactory when applied to a patent ductus and provide more room for manipulation. The first row of interrupted sutures is covered by a continuous suture on each vessel. It is important if the ductus is wide and short to dissect out and mobilize the aorta above and below the ductus as if for resection of a coarctation. If the ductus is very large it is wise also to open the pericardium in front of the vagus nerve in order to have the left pulmonary artery under direct observation and control in the event of difficulty.

Review of Surgical Material

In Hay and Ward's original series (1956) there were 108 cases and a further 120 are reported here, making a total of 228 cases of patent ductus arteriosus dealt with surgically. There were two deaths in the

* Manufactured by Messrs. Charles F. Thackeray & Sons, Ltd., of Leeds.

whole series, one being the case reported in the first series, where a reversed shunt was found to be present at operation (left to right shunt at previous catheterization) and the ductus was not tied. The second death occurred in the second series and was in a 13-year-old boy with a ductus 14 mm. in diameter and with considerable pulmonary hypertension. Division was successfully accomplished but convalescence was marked by a persistent systemic hypertension, the significance of which was not properly appreciated. He was readmitted 12 weeks after operation and died of uncontrollable haemorrhage during attempted surgical cure of an aneurysm at the site of resection. Autopsy showed that there was a coarctation of the aorta which had been outwardly marked only by a slight curvature of the vessel. This had been noted at the original operation but had not been thought to indicate any significant narrowing of the lumen. If the true situation had been understood it might have been possible to resect the coarctation at the original operation, but because the collateral circulation was undeveloped this may well have proved hazardous.

Other deaths have occurred after ligation of a patent ductus but only when the ductus was one of a group of complicated cardiac abnormalities. Only cases in which the patent ductus was the dominant lesion are included in the present series.

Table 1 gives the composition of the two series grouped according to the size of the ductus and also indicates the failure rate in each group. All cases in which the diameter of the ductus was 7 mm. or less were treated by ligation with or without transfixion suture. In our second series of 120 cases there were 69 in this group and the only failure was in an infant with a ductus 6.5 mm. in diameter and with exceptionally thin walls. Recanalization followed this operation and it may be that the sutures slowly cut through the thin vessel walls. Of 51 cases with a diameter of 8 mm. or more there were four recanalizations and three further cases have murmurs which are suggestive, though not diagnostic, of recanalization. The cases with definite recanalization had ductuses with original diameters of 9 mm. (two cases), 14 mm. and 15 mm.; those in which recanalization was suspected had diameters of 8 mm., 9 mm. and 11 mm. Although recanalization represents failure to achieve the aim of the operation, in all cases the condition of the patient had improved and the shunt appeared to be much smaller than before operation.

Method of Closure

In the first series the only method of closure employed was double ligation. Table 2 shows the

TABLE 2
OPERATIVE PROCEDURES FOR PATENT DUCTUS ARTERIOSUS, 1954-58 (SERIES 2)

Operation	Cases (No.)	Recanalization
Simple ligation	70	5 (+3?)
Ligation and transfixion suture	40	0
Division	10	0
Total	120	5 (+3?)

methods of closure adopted in Series 2. Simple ligation was employed 70 times with five certain and three doubtful recanalizations, ligation and transfixion suture in 40 cases with no recanalization, and division in 10 cases with no recanalization.

Taking the series of 228 cases as a whole it is clear that the risk of recanalization after simple ligation is very small indeed if the ductus is 7 mm. in diameter or less. There was only one example in 122 cases of this size treated in this way.

One hundred and six cases had a patent ductus 8 mm. in diameter or larger, and the situation with regard to these is shown in Table 3. It will be seen

TABLE 3
PATENT DUCTUS ARTERIOSUS OVER 8 MM. IN DIAMETER (COMBINED SERIES)

Operation	Size of Ductus (mm.)	Cases (no.)	Failure to Close	Recanalization
Simple ligation	8-10 Over 10	62 22	2 8	4 (+2?) 4 (+1?)
Ligation and transfixion suture	8-10 Over 10	9 2	— —	— —
Division	8-10 Over 10	3 6	— —	— —
Operation abandoned	8-10 Over 10	— 2	— 2	— —
Total		106	12	8

that 18 of these cases were not permanently closed after operation, a failure rate of 16%. All these failures were in cases treated by simple ligation. As before mentioned, the failure rate was especially high when the ductus was more than 10 mm. in diameter. Fewer than one in three of these cases (eight out of 22) could be closed by ligation, and recanalization followed in four others. Thus, simple ligation gave permanent closure in less than half of this group of 22 children with a large ductus treated by this method. In the intermediate size of 8 to 10 mm. six out of 66 cases (9%) were not permanently closed.

By contrast there were no failures and no recanalizations in 11 cases treated by ligation and

transfixion alone. The numbers are small and may not be really significant but they suggest that this technique may possibly give better results.

Nine cases in this group of large patent ductus were treated by division with a successful outcome in all except the one death from a hidden coarctation recorded above.

In our last 91 cases there have been no certain recanalizations, although the three doubtful examples are to be included among these. Of these 91 cases, 41 were ligated simply, 40 had an additional transfixion suture as described and 10 were divided. For what it is worth the doubtful recanalizations were all in the group of simple ligations.

Conclusion

Simple ligation is a safe and easy method of obliteration of the patent ductus when the diameter is 7 mm. or less. It may be even more secure if a transfixion suture is employed in addition. Above 8 mm. it seems clear that division should be the method of choice. Our second series of cases covers a transition period in our surgical policy but the failure rate of 4% (five in 120 cases) compares favourably with the previous figure of 14% (16 in 108 cases). Further reduction of the failure rate is probably dependent on more extensive use of division of the medium sized ductus. The overall mortality was 0.9% (two deaths in 228 cases).

Summary

Two hundred and twenty-eight cases of patent ductus arteriosus treated surgically are reviewed.

In 122 cases the ductus was 7 mm. or less in diameter; all were ligated with or without transfixion suture and there was only one recanalization.

In 106 cases the ductus was 8 mm. or more in diameter. In 18 (16%) cases closure was either not complete or not permanent. All failures occurred after simple ligation.

Simple ligation, preferably with a multiple transfixion suture, gives satisfactory closure of the small patent ductus (7 mm. or less in diameter).

Where the patent ductus is 8 mm. or more in diameter permanent closure can only be ensured by dividing it.

Most of the cases reported in this paper were under the care of Professor John D. Hay, and it is a great pleasure to record my indebtedness to him for his stimulating help, both in the clinical work involved and in the preparation of this report.

My thanks are also due to Dr. H. Gordon Farquhar, who referred many cases for operation; to Dr. Olive Scott and Dr. Gerard Gearty for their invaluable part in the diagnosis, post-operative care and follow-up of the patients; and to Miss Barbara Duckworth, medical artist, of the Department of Surgery, University of Liverpool, who made the drawings.

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VESICO-INTESTINAL FISSURE*

BY

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The great advances in paediatric surgery during the last two decades have brought about a change of attitude towards infants and children suffering from severe congenital malformations. A large number of these anomalies can now be satisfactorily treated and following the operation the child will be normal or nearly normal.

There are, however, still malformations or malformation complexes which are thought to be either untreatable or unjustifiable to treat as the child will remain more or less handicapped even after the most successful operation. These are mainly malformations of the central nervous or genito-urinary systems. It is my belief that in the next decade paediatric surgery will have to come to grips with these problems. We shall have to re-examine the contention that these children will never make useful members of society and are better left to die. We shall have to realize that with modern methods in physical education and rehabilitation much more can be done. This has been shown, for instance, in the management of spastic children. We shall also have to admit that with antibiotics and modern nursing care many of these children do not die or only die after a long time, a prolonged agony for them and their families alike.

I am prompted to this introduction because the condition which I am about to discuss is either not mentioned at all in the textbooks of paediatric surgery or urology or, if briefly described, it is dismissed as untreatable. There have been a few references in the literature to attempts at operation but as far as I can ascertain they have all ended in failure (Swan and Christensen, 1953). This prompts me to describe our experience in the treatment of this condition.

Definition and Description

The name vesico-intestinal fissure was introduced by Schwalbe in 1909, but the malformation has been

given a number of different names, such as ectopia vesicae with Meckel's diverticulum opening on the exposed bladder surface, extrophy of the bladder and colon, ectopic cloaca, etc. (Keith, 1908; Campbell, 1951; Williams, 1957).

In this condition there is an ectopia vesicae, which is often split into two lateral fields by an intervening zone of ectopic intestinal mucosa. If two kidneys are present, each ureter opens into the corresponding bladder field, but frequently one kidney is absent and malformation and displacement of the kidney is common. The intestinal mucosa belongs to the ectopic caecum. The opening of the appendix is often visible and the lower ileum tends to prolapse through the ileo-caecal valve forming a striking, bright red, sausage-shaped tumour. The colon is rudimentary and usually ends in front of the sacrum; the anus and rectum are always absent (Fig. 1). Duplication of some part of the lower intestine, such as the appendix or colon, is not infrequent. There is always an exomphalos situated above the ectopic intestinal field and a small myelo-meningocele or meningocele is frequently present; in one of our cases it only developed two months after birth.

The penis or clitoris is usually, although not invariably, split and the two halves widely separated. In one of our cases we were able to demonstrate, with the aid of serial sections of the autopsy specimen, that there were two complete penes each with a completely formed urethra, corpora cavernosa and spongiosa and prostate gland (Fig. 2).

Incidence

We saw our first case of vesico-intestinal fissure in 1953 and then considered it to be a great rarity. There are, however, a very large number of reports of this malformation in the literature since Meckel described the first case in 1812. In the last six years we have seen four cases as compared to 22 cases of ectopia vesicae and it appears quite possible that the condition is more common than is usually realized as many of the apparently hopeless children may not reach surgical centres.

* A paper read at a meeting of the British Paediatric Association held in Liverpool in June, 1959.

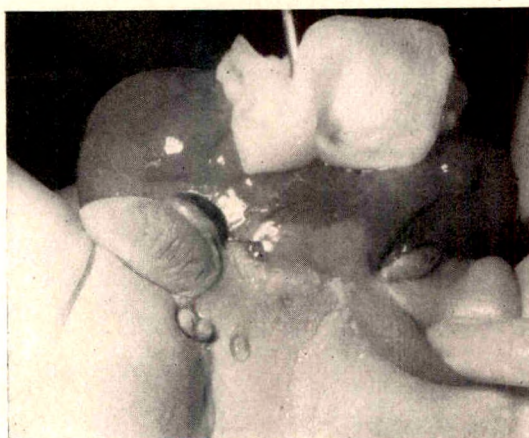


FIG. 1.—Perineal view. The two penes are clearly shown. There is no anus.

Embryology

Vesico-intestinal fissure has been of great interest to embryologists because the malformation throws some light on the embryology of the cloaca, the lower abdominal wall and the causation of ectopia vesicae. In this context it is impossible to give a detailed description of the various opposing views regarding the embryological aetiology of the condition which we discussed in a previous article (Hall, McCandless and Rickham, 1953). It suffices to state that the hypothesis recently brought forward by Patten and Barry (1952), and especially their resurrection of Keibel's (1896) view that the genital tubercles are primarily paired structures, has done much to explain most important features of this intriguing malformation (Fig. 3).

In the very early embryo the paired genital tubercles develop near the cephalic border of the cloacal membrane towards the end of the second week of intra-uterine life. They migrate towards each other and by the fifth week they fuse in the midline, reinforcing the cephalic border of the cloacal membrane (Fig. 3 (A₁, A₂, A₃)). It is thought that in ectopia vesicae the genital tubercles develop somewhat caudally to their normal position, approximately opposite the point where the urorectal fold comes to the surface. If they now fuse in the midline the genital orifice will be cephalic and the anal orifice caudal to them (Fig. 3 (B₁, B₂, B₃)). We developed this theory a stage further and assumed that if the paired genital tubercles develop still more caudally than with ectopia vesicae, they can now only fuse in the midline caudal to the cloacal membrane. There would then be a deficiency of secondary mesoderm over the whole of the

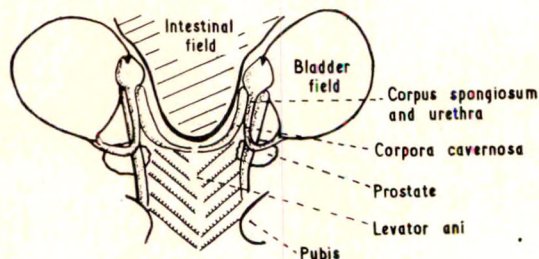


FIG. 2.—Schematic drawing of dissection of case shown in Fig. 1.

hypogastric area and the extensive cloacal membrane would break down. If the membrane ruptured immediately after the formation of the tailfold, it would expose the dorsal and lateral walls of the hindgut. As Johnston (1913) has pointed out, the whole of the gut distal to Meckel's diverticulum is derived from the hindgut. It will be seen that the above hypothesis explains the intestinal ectrophy and the frequent association with widely separated split penis or clitoris (Fig. 3 (C₁, C₂, C₃)).

Treatment

Some details of the treatment of our four cases may be of interest because these show all the pitfalls in the treating of this condition and also how we were able to learn from our mistakes.

Case 1. The first case, a boy weighing 5 lb., was admitted moribund and any active treatment was out of the question. He died on the third day. A careful post-mortem dissection enabled us to form a detailed picture of the pathological anatomy of the condition.

Case 2. One year later we saw a second almost identical case when a few hours old. This infant was grossly premature, weighing 3½ lb. At operation the extrophied intestinal field was excised and on entering the abdomen it was found that the whole of the distal colon was duplicated (Fig. 4). This too was excised and the lower end of the ileum was pulled through to the perineum (Fig. 5). The two ectopic bladder fields were then united in the midline, the small exomphalos was repaired and the abdomen closed (Fig. 6). The infant stood the operation well, but it soon became apparent that the remaining length of the intestine was insufficient for adequate food absorption. In spite of numerous blood transfusions, plasma, protein hydrolysate and

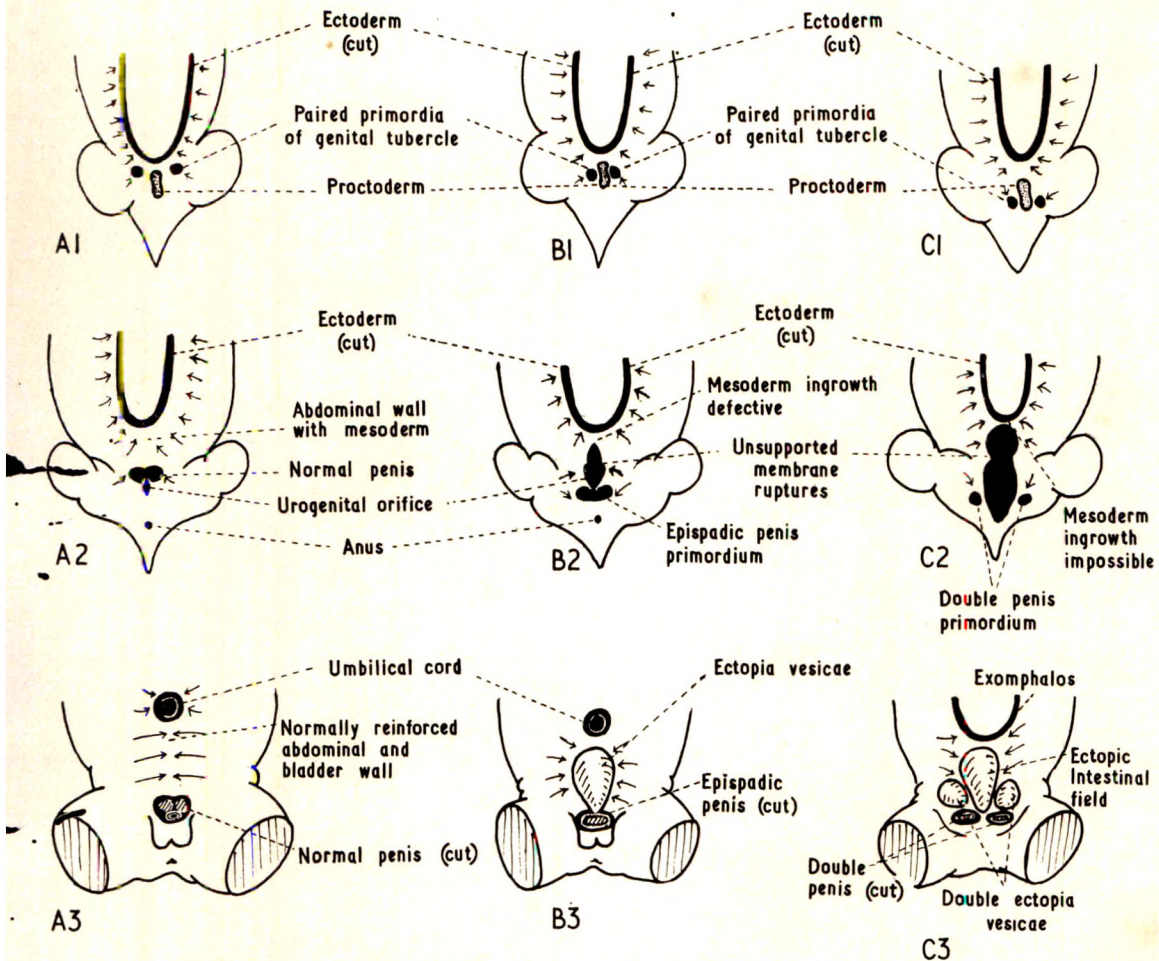


FIG. 3.—Diagrammatic representation of the development of the infra-umbilical abdominal wall in the normal foetus (A), and ectopia vesicae (B). The development of vesico-intestinal fissure can be explained on the same basis (C).

sugar infusions, feeding by intragastric drip of high calorie, high protein concentrates, etc., the infant did not gain weight, continuously passed numerous fluid undigested stools and finally died two months after operation. Since then an identical case, that of Koop (1957), has come to our notice. This child also failed to thrive because of lack of absorption of sufficient nutriment. As these infants were only deprived of their colon and lowest ileum it is somewhat difficult to explain why they did not absorb sufficient food unless their gross prematurity had something to do with this deficiency.

Case 3. The third infant with vesico-intestinal fissure, another premature boy weighing $4\frac{1}{2}$ lb., was admitted six months later (Fig. 7). Bearing in mind our unfortunate previous experience, we carefully preserved the ectopic intestinal field with its blood supply and closed the everted caecum and ascending colon. The distal colon, ending blindly in front of the sacral promontory,

was freed and drawn down to the perineum. The two bladder fields were then closed in the midline as before. The exomphalos in this case was, however, a very large one and having already taken up most of the slack of the abdominal wall by suturing the bladder fields together, it now became absolutely impossible to cover with skin the abdominal defect produced by excision of the exomphalos. After several unsuccessful attempts at closure had been made, a piece of sterile nylon sheath was sutured to the mobilized abdominal skin across the defect. To our great surprise the child stood the operation quite well and when the nylon sheath finally separated two weeks after operation, there was granulation tissue underneath it, retaining the intestine inside the abdominal cavity (Fig. 8). Unlike Case 2, this infant thrived, the number of stools was not too excessive and he gained weight satisfactorily. The area of granulation tissue was covered by split skin grafts, and when 3 months old the child had doubled his birth weight.

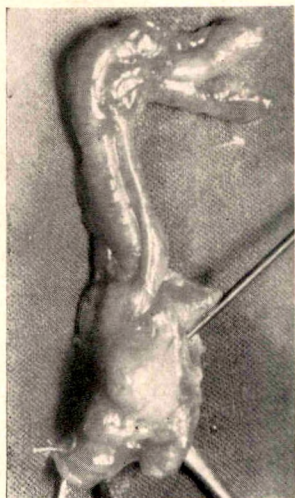


FIG. 4

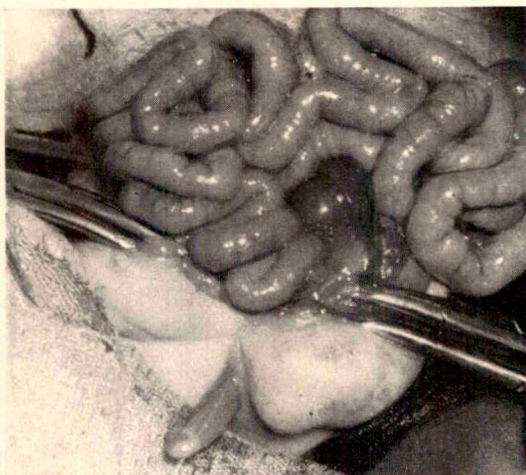


FIG. 5

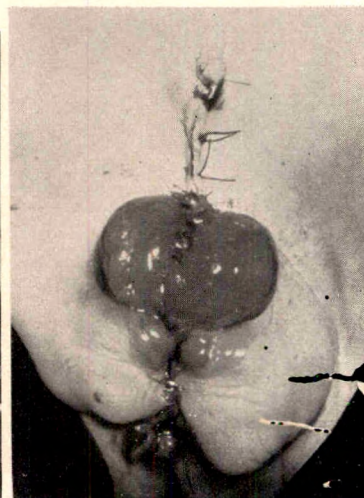


FIG. 6

FIG. 4.—Excised specimen from Case 2. The duplicated ascending colon, hepatic flexure and rudimentary double transverse colon are shown.

FIG. 5.—Case 2. The terminal ileum has been pulled through a hole made in the perineum.

FIG. 6.—Case 2. At end of operation.

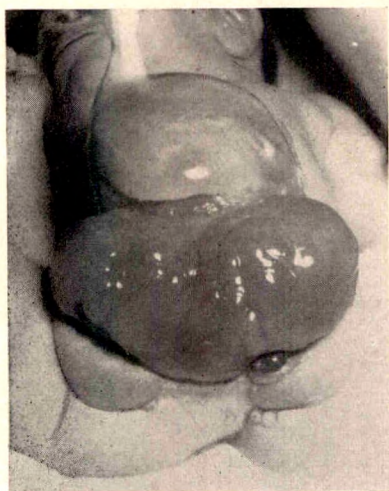


FIG. 7.—Case 3. Note large exomphalos.



FIG. 8.—Case 3. After separation of nylon sheath.

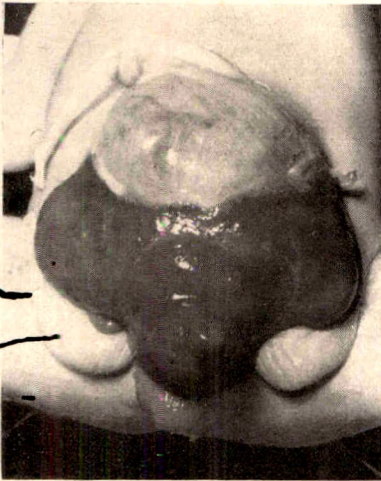


FIG. 9.—Case 4.

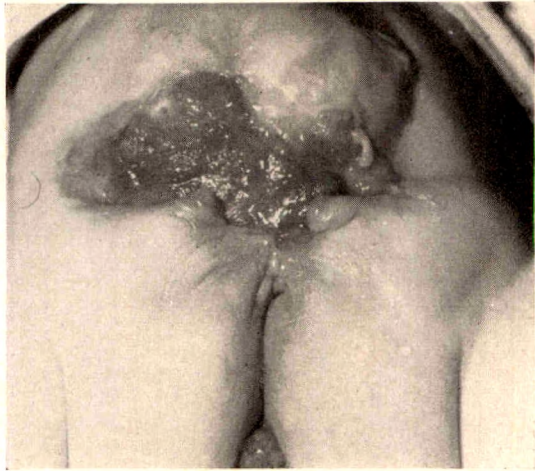


FIG. 10. Case 4, aged 1 year. Note incisional hernia.

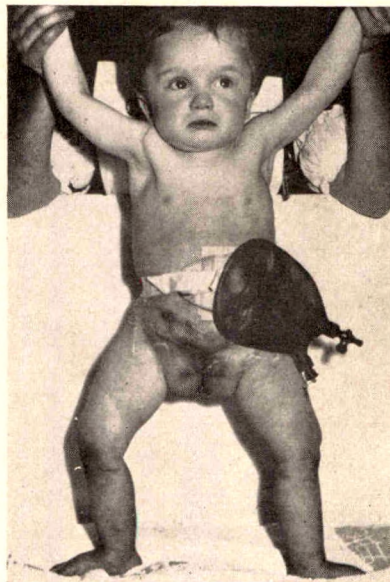


FIG. 11.—Case 4, aged 20 months, wearing urinary bag.

He then developed acute mechanical intestinal obstruction and, as conservative treatment was of no avail, his abdomen was opened. As was to be expected, the whole of the small intestine was glued together and closely adherent to the anterior abdominal wall. Only with the greatest difficulties was it possible to relieve the obstruction by dividing numerous adhesions. Although the child recovered from the operation, he had two further attacks of acute intestinal obstruction during the next three weeks, each of them necessitating a laparotomy. He finally died following the third laparotomy.

Case 4. We were somewhat disheartened by this experience and when a fourth case presented 18 months ago we devised a new plan of attack. Instead of opening the abdomen by incising the amnion covering the exomphalos, we now decided not to touch the exomphalos at all, but to enter the abdomen through the opening made by dissection of the intestinal field. We then wanted to proceed as in Case 3, repairing the caecum and pulling the terminal colon down to the perineum, and to close the abdomen by uniting the two ectopic bladder fields. If we found that there was sufficient abdominal wall and skin we would repair the exomphalos; if not, we would treat the exomphalos conservatively, employing Grob's (1957) method.

This child, a boy weighing $5\frac{1}{2}$ lb., born on August 17, 1957, had a medium-sized exomphalos, a split penis and a small sacral myelo-meningocele (Fig. 9). His legs moved well, both testicles were undescended. At laparotomy on August 18, he presented a picture identical with that of Case 3 with the exception that he had only one kidney, which was situated in the pelvis and had a very short ureter running to the left half of the ectopic bladder. After the bladder fields had been united it was found that there was enough slack in the abdominal wall to allow a complete repair of the exomphalos. The child stood the operation well. The post-operative period was complicated by an attack of mechanical obstruction when the child was $2\frac{1}{2}$ months old. At laparotomy several adhesions had to be divided. The child made an uninterrupted recovery, gained weight slowly but steadily and started to stand up when 14 months old. He had a large incisional hernia (Fig. 10). There was no faecal continence, his perineal colostomy acting twice a day.

On February 20, 1959, it was decided to cut the left ureter off the ectopic bladder and, if possible, to perform a cutaneous ureterostomy in the left iliac fossa. At operation it was found that the length of the ureter was only about $1\frac{1}{2}$ in. An end-to-end anastomosis between the ureter and a segment of isolated left ileum was therefore performed. In order to do this and to use as short an isoperistaltic piece of ileum as possible, it was necessary to rotate the ileal segment and mesentery through 180° , and to bring the loop out in the left iliac fossa. The dissection was made rather difficult by the

numerous intra-peritoneal adhesions, but it was possible to rotate the loop without interference to its blood supply and to bring a $3\frac{1}{2}$ -in. long segment of ileum out in the left iliac fossa. Although the kidney is now draining urine practically straight upwards, there has been no stasis, and no hydronephrosis has developed. There is hardly any residual urine in the isolated ileal loop, possibly because of the vigorous peristalsis of the segment of intestine.

On April 23, 1959, the two ectopic bladder fields were excised and, after mobilization of the skin, it was possible to suture the wound under some tension. Most of the wound healed by first intention, but a small area in the centre sloughed. At the same time the two corpora cavernosa were divided from the widely separated pubic bones and the two penile halves were without difficulty brought together in the midline. No attempt was made to unite these two halves, but the posterior urethra and a small part of the vesical trigone were repaired.

The boy is now 22 months old and very well. He walks well, talks and appears of normal intelligence. He wears the infant's ileostomy urinary bag previously described (Rickham, 1956, 1958), and can be kept dry for two days at a stretch (Fig. 11). He is incontinent of faeces, but, in our experience, faecal incontinence is not a very great problem when the child gets older, and with the aid of a suitable diet, enemata and training it should be possible to keep him clean. He has intelligent parents and, with luck, his progress should be satisfactory.

In conclusion it should be said that vesico-intestinal fissure, the most severe malformation of the lower urinary tract, is perhaps not as rare as was previously supposed. After trial and error and committing (in retrospect) several stupid mistakes, we believe that the treatment outlined above may prove successful in the majority of cases and that the end result may well produce a useful member of the community.

Miss Isabella Forshall operated on Case 2 and kindly permitted its inclusion in this paper.

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LE MESURIER'S OPERATION FOR HARE LIP*

BY

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This is a report on hare lip operations performed by the method of le Mesurier (1949). Since 1955 we have done 238 operations on hare lips in the Children's Hospital in Munich. In 98 cases there were unilateral complete hare lips, in 27 cases bilateral complete hare lips. I shall discuss only the primary plastics and not the corrections which are often necessary, and I shall not mention the problem of cleft palate in spite of its connexions with hare lip.

We began in 1957 to operate on total palatoschisis in two stages. In the first operation at the end of the second year we close the soft palate, and the residual cleft is closed before the child starts to go to school. In the meantime we try to diminish the extent of the residual cleft by using a so-called stimulation plate, a method which is described by Schweckendiek (1955), McNeil (1956), and Derichsweiler (1958), but our experience with the stimulation plate is as yet insufficient to form any judgment.

In total unilateral hare lip we have to span the fissure not only in the frontal but also in the sagittal plane. There is no difficulty in closing the gap in the frontal plane, even if it is a very large one, but it is sometimes difficult to close the gap in the sagittal plane. As the two edges of the cleft are in different planes there results an oblique position of the nostril and the columella and a flattening of the wing of the nose at the side of the gap.

There are two problems in hare lip operations, the lip and the nostril. I think we should try at the first operation to undertake the corrections as far as possible, but the plastics of the nostril must not complicate and prolong the operation too long. I therefore postpone the plastics of the tip of the nose and the columella until later, if such correction is necessary at all. It is known that the likelihood of spontaneous correction is much greater in early childhood than later on.

Fig. 1 shows the original method of le Mesurier. At the outermost left side of the picture the final

point of the medial incision and the centre of the upper lip do not coincide, but lie a few millimetres nearer to the cleft. The cause for this asymmetry following le Mesurier's operation is the difference in height of the lip on the normal side and the abnormal side. This causes a slight displacement of Cupid's bow towards the side of the cleft except in those rare cases where Cupid's bow is situated on the medial side of the gap.

Fig. 2 shows the incisions in total hare lip. The plastics of the base of the nose we do by the method of Axhausen (1936), using the mobilized flaps of the mucous membrane. We make a transverse incision at the base of the inferior nasal concha to put the lateral part of the cleft forward in the sagittal plane (Fig. 3). The starting points of the incisions we place a little in front of the nostril to have as much material as possible for the base of the nose. To ensure that the vertex of Cupid's bow is in the middle of the lip, the foot point of the medial incision is placed in the calculated middle of the demarcation line of the red border, even if the length of this medial incision is longer than normal, i.e. more than 8 mm. If a good cosmetic result is risked by this procedure we can do a longitudinal correction by excision of a triangle. On the lateral part of the cleft the length of the incision is 8 mm. It is very important that the incisions which form the later flap are exactly half as long as this longitudinal incision and exactly as long as the cross section on the longitudinal medial incision. The angle between the longitudinal and transverse incisions should be 90° . If a longitudinal correction on the lateral side of the cleft is necessary, this can be done by taking off a wedge at the insertion of the nose wing. With regard to the plastics of the wing of the nose, we do not undertake a dissection of both layers (mucous membrane and skin). If a dissection of the cartilages is necessary for a correction of the tip of the nose, for instance, it is very difficult if there has been any lesion of the cartilage in early childhood. The first correction of the sinking in of the side of the nose we do by a Z-plastic. Figs. 4 and 5 show the result of operation.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.



FIG. 1.—Original in *Chirurgische Operationslehre* B. Breitner, Printed in Austria, Copyright by Urban and Schwarzenberg-Wien. Vol. I, Fig. 4 d-e, p. 11.

In operations for total bilateral cheilognathouranoschisis, the greatest problem is the prominence of the premaxilla. Browne (1932) has pointed out that we must put the premaxilla in the alveolar curve and must not try to put the lateral parts of the cleft forward. Matthews (1955) was also of this opinion. We agree with Matthews that the repositioning of the premaxilla should be done as a

dilatation (Figs. 7 and 8). Within a very short time the gap is wide enough to start resection of the prevomer bone, as described by Browne (1932). It is very necessary to prevent the premaxilla from tilting inside; we prefer the teeth to stand out a little. For fixation of the premaxilla we use fragments of bone placed at both sides of the premaxilla in the alveolar curve and fix it with small

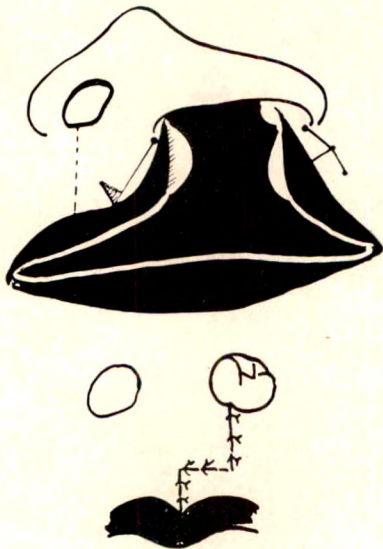


FIG. 2.

single operation, but not in the same session as the plastics of the lip. In many cases the gap between the two alveolar processes is smaller than the premaxilla. Therefore we first have to make an extension of the gap. This is done by means of a plastic plate with a screw (Fig. 6); it is quite easy to put the premaxilla in the alveolar curve after the

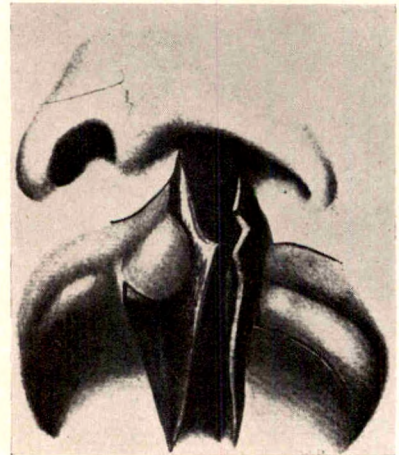


FIG. 3.—From *Chirurgische Operationslehre* B. Breitner, Vol. I, p. 22.

flaps of mucous membrane (Fig. 9). We use the bone obtained in the resection of the premaxilla, divided into two pieces. We perforate the premaxilla and fix it with a piece of Kirschner wire in the sagittal direction; then we mobilize the mucous membrane of the alveolar process and the premaxilla, put the fragments of bone in small fissures

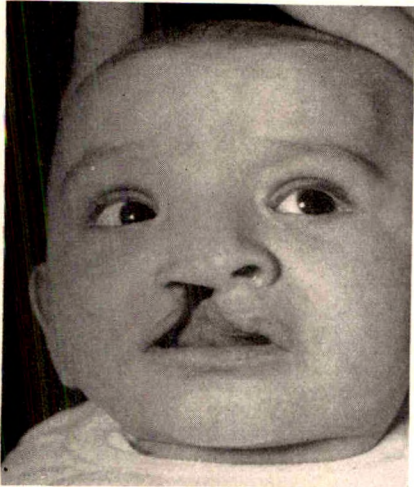


FIG. 4.—Unilateral total hare lip before operation.

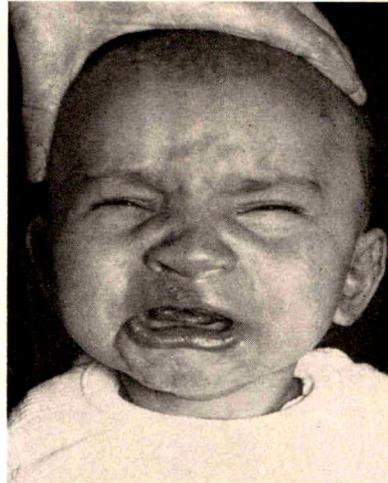


FIG. 5.—Unilateral total hare lip (same case as shown in Fig. 4) after operation.



FIG. 6.—Extension of alveolar gap with plastic plate.

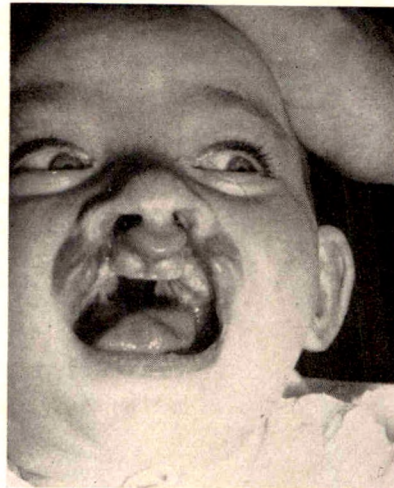


FIG. 7.—Gap between two alveolar processes is wide enough; pre-maxilla is reduced.

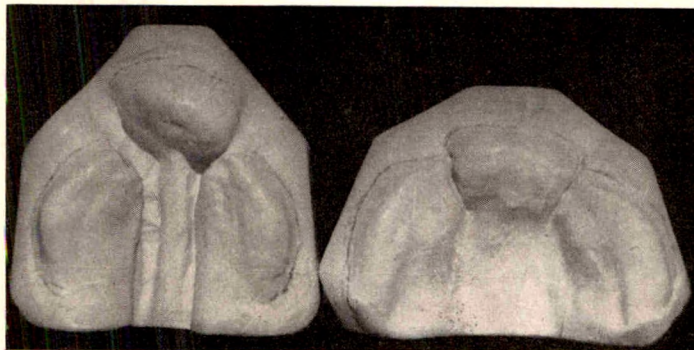


FIG. 8.—Plaster casts before and after repositioning of premaxilla.

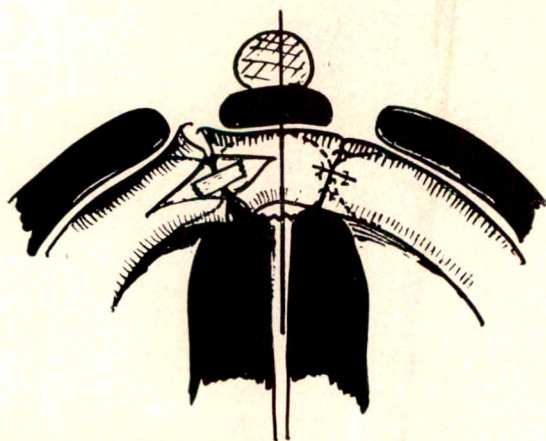


FIG. 9.—Diagram showing effect of resection of prevomer bone; premaxilla is fixed with a piece of Kirschner wire and with fragments of bone.

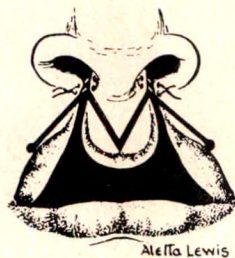


FIG. 10.—Operation for bilateral total hare lip by Denis Browne (*Ann. Royal Coll. Surg. England*, Vol. 5, Sept. 1949).

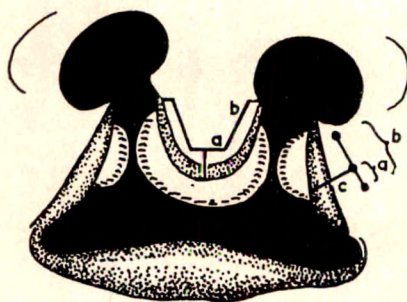


FIG. 11.—Le Mesurier's method at operation for bilateral total hare lip.

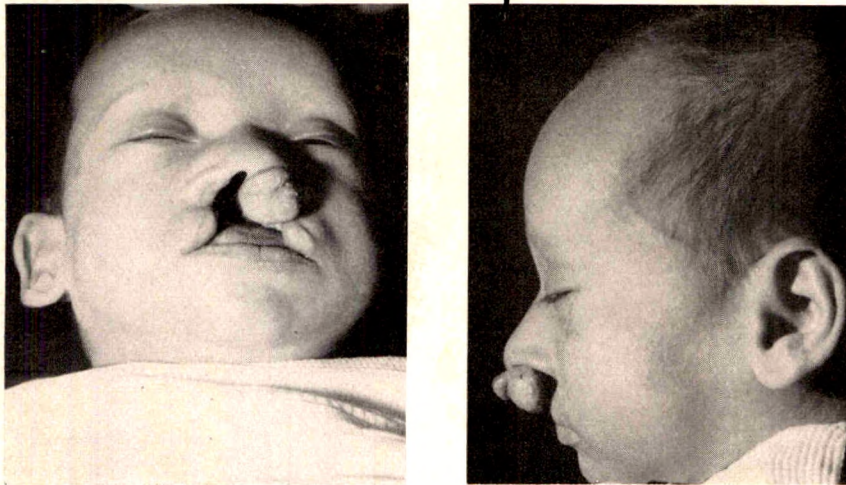


FIG. 12.—Bilateral total hare lip before reposition of premaxilla.

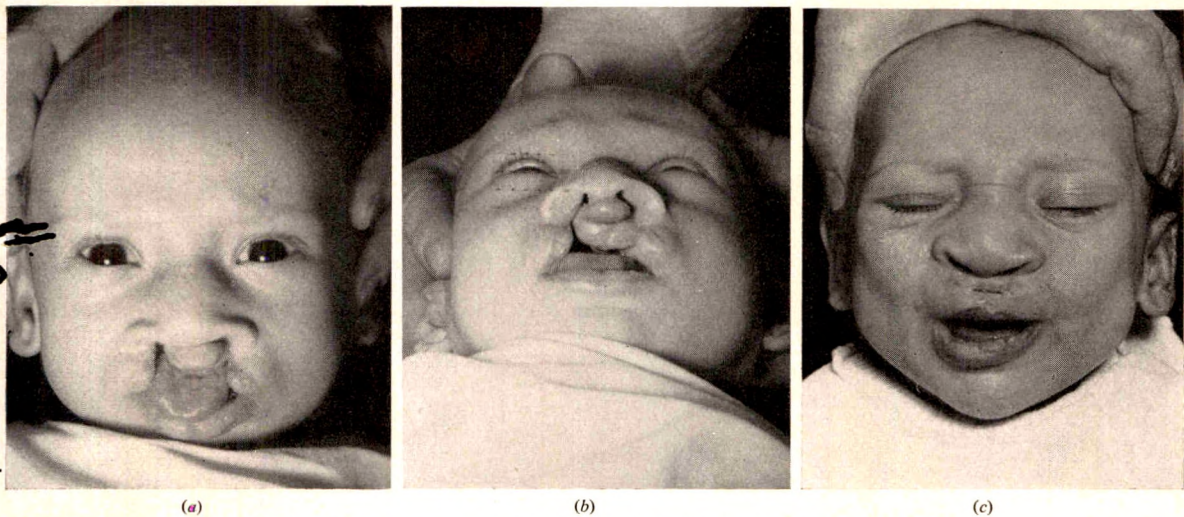


FIG. 13.—Same case as shown in Fig. 12: (a) and (b) after reposition; (c) after operation.

and make a suture in the mucous membrane. In this way, in the majority of cases it is possible to place the premaxilla in the alveolar curve.

The closure of the hare lip we try to do in one session (Figs. 10 and 11). We use the method of Browne if we have a sufficient amount of material, but if we have only a small middle segment we try separation of the lateral parts of the cleft by the method of le Mesurier.

Figs. 12 and 13 show the result of the operation on a case of bilateral hare lip at the Children's Hospital, Munich.

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CLINICAL MANIFESTATIONS OF PRIMARY HYPEROXALURIA*

BY

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Primary hyperoxaluria is characterized during life by a continuous urinary oxalate excretion level of about 100-400 mg. (expressed as $(\text{COOH})_2 \cdot 2\text{H}_2\text{O}$) per 24 hours as opposed to the normal value of less than 45 mg. per 24 hours. Patients with this disease usually present in early childhood with multiple bilateral renal or ureteric calculi which increase rapidly in size and are composed wholly or predominantly of calcium oxalate. Nephrocalcinosis, recurrent attacks of pyelonephritis and hypertensive damage destroy the renal parenchyma and the patients usually die from renal failure later in childhood. Descriptions of cases in which the diagnosis was confirmed chemically during life and which conformed to this clinical picture have been published by Newns and Black (1953), Aponte and Fetter (1954), Archer, Dormer, Scowen and Watts (1957), Godwin, Fowler, Dempsey and Henneman (1958) and Hodgkinson (1958). The characteristic post-mortem findings are widespread destruction of the renal parenchyma by aggregates of calcium oxalate crystals, and similar deposits in the tunicae mediae of the small muscular arteries and arterioles, the myocardium, and the testis (especially the rete testis) in association with the bone trabeculae and at the growing ends of the long bones (Scowen, Stansfeld and Watts, 1959). The term oxalosis (Dunn, 1955) conveniently describes this condition of disseminated extra-renal calcium oxalate deposits.

Mulloy and Knutti (1951), Neiman, Rauber, Pierson and Gentin (1957) and Katzuni and Sandbank (1959) reported cases of infants who died apparently from renal failure at the age of a few months and in whom the findings of calcium oxalate nephrocalcinosis without stones, and of oxalosis also in Katzuni and Sandbank's (1959) case, suggest that they may have been cases of primary hyperoxaluria in which the disease followed an unusually fulminating course. Zollinger and Rosenmund (1952), Lund and Reske-Nielsen (1956) and Öigaard and Söderhjelm (1957) describe the post-mortem findings in

cases which may have been examples of primary hyperoxaluria in which stone formation began at an unusually late age. The urinary oxalate excretion was not measured in any of these cases.

The purpose of the present paper is to describe in detail the clinical features of a group of eight cases of primary hyperoxaluria arising in three families, and to comment on some aspects of the natural history of the disease. The results of an investigation of the genetic aspects of the disease, which was based on these and two other families, have been published elsewhere (Scowen, Watts and Hall, 1959) and the families have been numbered serially from four onwards in order to facilitate cross reference to that paper. Three previous families (numbers 1-3) had been investigated and the results recorded (Archer, Dormer, Scowen and Watts, 1958) before the present cases, which provided proof of some of our earlier hypotheses, became available for study.

Case Reports

Family 4. In this family there were 12 children, one dying in infancy of unknown cause. The parents are not related, and they, the unaffected children and other relatives have normal urinary oxalate excretions.

CASE 1. A boy, the second child, was admitted to hospital at the age of 10½ years because of right-sided intermittent abdominal pain, vomiting and haematuria of one day's duration. He had had a similar episode a few months previously, which had resolved without treatment. The present attack subsided spontaneously, but bilateral renal and ureteric calculi were demonstrated radiologically. He remained in hospital for two and a half months and was symptom-free except for one attack of renal colic. During this period his urine, which had initially contained leucocytes, erythrocytes and a trace of albumin, but had remained sterile on culture, became normal. The Sulkowitch test showed a low excretion of calcium, and the amino-acid pattern was normal. The blood urea was at first elevated to 49 mg./100 ml. but the serum sodium, potassium, chloride, CO_2 combining power, protein, calcium, phosphorus and alkaline phosphatase were normal.

Three months later an attack of left-sided renal colic was accompanied by the passage of a calculus, and laboratory tests gave results similar to those obtained previously. An intravenous pyelogram after this episode

* This article includes material given in a paper to the 6th Annual Meeting of the British Association of Paediatric Surgeons in June, 1959, by one of us (E.G.H.).

demonstrated mild bilateral hydronephrosis with slight impairment of dye excretion. Calculi were seen on both sides.

During the next 15 months he had only one mild attack of colic and then passed two small calculi which on analysis were found to consist almost entirely of calcium oxalate. The urine contained a variable slight excess of leucocytes, was usually sterile on culture and the blood urea remained below 40 mg./100 ml.

A high urinary oxalate excretion was demonstrated in March, 1958, and although he had remained in apparent good health for the previous two years, he was readmitted for further study. There were no abnormal clinical findings: marrow aspirate did not show any oxalate deposits, and the eyes were normal on slit-lamp examination. A radiograph of the kidneys showed multiple bilateral stones; there was no abnormality in the appearance of the long bones nor visible calcification in the testes. Laboratory examinations showed a sterile acid urine with excess of leucocytes, a blood urea of 45 mg./100 ml. and urea clearance of 80% with normal figures for blood sodium, potassium, chloride, CO_2 combining power, calcium, phosphate, uric acid and total protein. There was a moderate fall in serum albumin and a rise in globulin, principally gamma globulin. A series of 24-hour urine specimens showed a daily oxalate excretion in the range of 400-490 mg.

At the age of 15½ years, nine months after this admission, he had further left-sided colic, and three months later, although he had passed several calculi, it was necessary to admit him for removal of impacted calculi at the lower end of the left ureter. He had lost some weight, developed marked polyuria and anaemia, but felt fairly well. His blood pressure was 130/100; intravenous pyelography showed gross impairment of renal function and left-sided hydronephrosis, and his blood urea had risen to 100 mg./100 ml. His urine remained sterile but was loaded with leucocytes. At operation three calculi were removed from the distended left ureter. Post-operatively his blood urea rose to 292 mg./100 ml., falling gradually to its present level of 220 mg./100 ml. two months after operation. He has developed a marked anaemia and acidosis, and his daily oxalate excretion, which during the three weeks after operation ranged from 218-320 mg. with urine volumes ranging from 1,800 to 3,300 ml., has now fallen to about 100 mg.*

Calculi were analysed on several occasions and consisted entirely or mainly of calcium oxalate.

CASE 2. A girl, the third child, was investigated at the age of 13½ years because her daily urinary oxalate excretion was 202-214 mg. She had never had any urinary symptoms and was quite well. Physical examination was negative, and radiography did not show any evidence of nephrolithiasis. There were no calcium oxalate crystals in an aspirated sample of bone marrow, and no crystalline deposits could be demonstrated in the eyes by slit-lamp examination. Blood urea, urea clearance, total protein, calcium, phosphorus and uric acid values were normal;

the Sulkowitch reaction of the urine was Grade I, and the urinary amino-acids were normal. There was a slight increase in the serum γ , α_2 and β_1 globulins. She has been well for the last year, and oxalate excretion has remained at its initial high level.

CASE 3. A girl, the fourth child, was first admitted to hospital at the age of 7½ years with a two-day history of vomiting, colicky right-sided abdominal pain and anorexia. She had never been ill before. Radiography showed a large right kidney with numerous stones in both kidneys and ureters. The urine was acid with a slight excess of leucocytes and free of pathogenic organisms. The initial blood urea was 145 mg./100 ml. She improved during the next two weeks: further biochemical and radiological examinations did not reveal any evidence of a primary cause for her nephrolithiasis. She passed normal amounts of urine of low specific gravity, and her blood pressure remained within normal limits. Because of a further attack of colic a series of operations on the left kidney and ureter were performed for the removal of stones and she was discharged in fair condition three months after admission, her blood urea having fallen to 25 mg./100 ml. Analysis of the calculi showed the presence of calcium, phosphate and oxalate.

She was readmitted in uraemia a month later, but oliguria persisted in spite of treatment and she died 10 days later. Permission for autopsy was refused. Estimation of urinary oxalate was never performed.

CASE 4. A boy, the eleventh child, was seen at the age of 4½ years because urine examination had shown that he was excreting increased amounts of oxalate. He had not had any urinary symptoms and was perfectly well. Physical examination was negative. Radiography showed small left-sided renal and ureteric calculi. Marrow aspiration and slit-lamp examination did not show any evidence of oxalosis.

Blood urea, urea clearance, total serum protein, calcium, phosphorus and uric acid were normal. The urine gave a Grade I Sulkowitch reaction and the amino-acids were normal. Several oxalate determinations fell within the range 110-130 mg. per day.

Shortly after discharge from hospital he complained of left-sided pain, followed by the passage of a stone consisting entirely of calcium oxalate. He is now 5½ years old and has had no further symptoms, but his oxalate excretion remains high.

CASE 5. A girl, the twelfth child, was first seen at the age of 15 months because she had passed three small urinary calculi. There was no history of previous urinary disturbances. Physical examination was non-informative; the urine was acid and contained a slight excess of leucocytes; blood urea, total protein, sodium, potassium, chloride, CO_2 combining power, calcium, phosphate and alkaline phosphatase were normal. A radiograph of the abdomen showed a calculus in the right renal pelvis.

She was admitted for slit-lamp examination of the eyes and marrow aspiration, both of which were normal, and for further biochemical tests. The relevant urinary findings were a Grade I Sulkowitch reaction and an oxalate excretion in the range 90-110 mg. per day. The

* This patient died from renal failure three months after operation; terminally, he became oliguric and uraemic, and his urinary oxalate excretion decreased further.

blood estimations mentioned above, the urea clearance and urine amino-acids were found to be within normal limits. A further radiograph three months later showed a stone in the left renal pelvis, but she remained symptom-free for a year until she had another attack of renal pain, following which radiography showed that the calculus on the left side had disappeared. Occasional urinary oxalate estimations during the last year have shown results comparable with those quoted above.

Family 5. In this family there are two children only. The parents are not related, and they and other relatives tested do not show hyperoxaluria.

CASE 6. A girl, the first child, now aged 8 years, had painless haematuria at 2 and 3 years of age. At 5 years she had an episode of haematuria with abdominal pain and vomiting, and on radiography was seen to have bilateral renal stones and stones in the right ureter. On admission there were no abnormal physical signs and her blood pressure was normal. The urine was acid, free of cells and protein and sterile. The Sulkowitch reaction was Grade I and the amino-acids normal. Blood urea, total protein, sodium, potassium, chloride, CO_2 combining power, calcium, phosphorus and alkaline phosphatase were within normal limits. Radiographs of long bones were also normal.

Three calculi, consisting of calcium oxalate and a little phosphate, were removed from the lower end of the right ureter and she was discharged fit.

Re-investigation six months later was unhelpful, but at 6½ years she had a further attack of haematuria and the left renal stone was passed. Urine specimens tested for oxalate at this time showed increased values and she was accordingly readmitted at the age of 7 years for further investigations. There was little change in the renal opacities; bone marrow aspirate was normal and slit-lamp examination did not reveal any crystalline ocular deposits.

In addition to the tests mentioned above, the urea clearance, uric acid and serum protein electrophoresis were normal but the urine oxalate excretion averaged 170 mg. per day.

She has been followed for a period of one year and has remained well except for the passage of a stone and a mild attack of renal colic. The urinary oxalate excretion remains at its previous level.

CASE 7. A boy, the second child, now 6 years old, at 2 years developed retention of urine which was relieved by the removal of a stone from the urethra. He has since been symptom-free and was seen initially at 4 years of age, when there was no radiological evidence of nephrolithiasis.

He was admitted to hospital with his sister, and the same investigations were performed. All were normal except for the urinary oxalate excretion, which averaged 165 mg. a day.

Family 6. In this family there were four children and the parents are first cousins. The unaffected children, the parents and other relatives have normal oxalate excretions.

CASE 8. A boy, the first child, was first seen elsewhere at the age of 6 years because of nocturnal enuresis, frequency and polyuria of some duration. He had recently been rather lethargic. Physical examination and urine tests were negative, but a radiograph showed bilateral abdominal shadows thought to be calcified glands. He was then lost sight of until four years later when he was admitted to hospital with acute retention. He had had one previous such episode three years previously and the frequency and nocturnal enuresis had persisted.

He was undersized but otherwise appeared normal. His blood pressure was 120/80 and his blood urea 84 mg./100 ml. Shortly after admission he passed a stone and some gravel which were found to consist of calcium oxalate. As radiography showed bilateral renal stones he was transferred to Liverpool. Urine examination was normal but his blood pressure had risen to 130/100 and his blood urea to 110 mg./100 ml. Total serum protein and CO_2 combining power were slightly low, but serum chloride, calcium and alkaline phosphatase were normal. The phosphorus figure was a little high. A radiograph showed multiple bilateral and renal calculi with small kidney shadows, a right ureteric and two vesical calculi. The long bone structure appeared normal. He was operated upon and several calculi were removed from the small right kidney. Estimation of urinary oxalate at this stage revealed a high excretion (212 mg. per day). The urine amino-acid pattern was normal.

A month later his blood pressure had risen to 150/100 and his blood urea to 250 mg./100 ml. The vesical stones were removed at laparotomy but his subsequent course was one of slow deterioration with rising blood pressure and blood urea. Slit-lamp examination of the eyes was normal early in this terminal phase. During the fortnight before death his urine volume diminished and his urinary oxalate output fell to below 35 mg. per day. He died in uraemia 10 weeks after his transfer and autopsy was not permitted. Bone marrow aspirate taken after death contained no calcium oxalate crystals but post-mortem cerebrospinal fluid contained 0.42 mg. of oxalate per 100 ml.

Discussion

These are all classical cases of primary hyperoxaluria, except for Case 2 who has no urolithiasis although she is now almost 14 years old. The urinary oxalate excretion values are all between about 100 mg. per 24 hours and 400 mg. per 24 hours, and the individual values cannot be correlated with the severity or the apparent age of onset of the urolithiasis. The urinary oxalate excretion decreases during the last weeks of life as the terminal uraemic illness progresses, and we think that this may be associated with a phase of rapid oxalate deposition in the kidneys with the accumulation of at least the major proportion of the extra-renal deposits. The absence of detectable oxalate deposits

in the kidneys of patients with primary hyperoxaluria several years before death and in scarred pyelonephritic areas of the kidneys of one patient at autopsy (Scowen, Stansfeld and Watts, 1959; and unpublished observations), as well as the apparently normal bone development, except possibly when there has been prolonged renal failure, in spite of the calcium oxalate deposits at the growing ends of the bones at autopsy, are in conformity with this suggestion. Direct evidence of oxalosis during life was not obtained by sternal marrow aspiration biopsy or by slit-lamp examination of the eyes. It may be that trephine-biopsy of a cancellous bone or biopsy of a small muscular artery would be more informative in this respect.

Oxalosis only occurs if renal failure is accompanied by an abnormally increased endogenous oxalate production. There is no satisfactory method for the measurement of the blood oxalate level (see for example Barrett, 1943), but the observation that detectable amounts of oxalate were present in the cerebrospinal fluid and pleural effusion of the case reported by Scowen, Stansfeld and Watts (1959) and in the cerebrospinal fluid in Case 8 suggests that the concentration of this anion may be raised in the body fluids generally in the terminal stage of the disease.

Except for evidence of renal failure, the elevated urinary oxalate excretion was the only abnormal pathological finding in all of these patients. The value of this relatively simple diagnostic procedure in differentiating primary hyperoxaluria from other causes of juvenile urolithiasis, which do not carry such a grave prognosis, merits emphasis: Case 4 was diagnosed by this means before he presented with the clinical manifestations of renal calculi. Cases 1 and 8 illustrate the inexorable course of the disease and the failure of surgical intervention to influence its uniformly bad prognosis. All of our patients who were investigated in the pre-uraemic stage of the disease had normal serum uric acid levels. This is of interest in view of Aponte and Fetter's (1954) suggestion that the hyperuricaemia, which they observed in three cases with renal impairment, indicated that the disease was in some way associated with an abnormality of purine metabolism.

Although there are no reported cases of primary hyperoxaluria in patients whose urinary oxalate excretion was measured immediately after birth, there are clinical and pathological grounds for suggesting that the underlying error in the disease may be present at that time. The multiple incidence of the disease within sibships (Families 4 and 5 of this report) in the absence of any abnormality in the parents or more remote relatives, and the occurrence

of one consanguineous parentage in the total of eight families which have been studied in our laboratories (Archer *et al.*, 1958; Scowen, Watts and Hall, 1959) are compatible with the disease being due to the operation of a rare recessive character; the two sexes appear to be equally affected both in number and severity. However, Shepard, Krebs and Lee (1958) reported a family in which hyperoxaluria was present in two and possibly three successive generations, suggesting a dominant type of hereditary pattern. It may be that this apparently dominant type of inheritance resulted from the mating of a subject who was homozygous for the recessive gene with the corresponding heterozygous subject (cf. Garrod's (1908) explanation of the apparently rare dominant type of inheritance of alkaptonuria). If this were so, it is curious that the presumably homozygous parent does not show any evidence of stone formation. An alternative explanation is that there are two different metabolic lesions which cause excessive oxalate excretion and that each has its own pattern of inheritance. There is evidence that a metabolic error involving one of the pathways of glycine metabolism results in excessive endogenous oxalate production in cases of the type which we have described (Watts, Scowen and Crawhall, 1959).

Summary

The clinical features of eight cases of primary hyperoxaluria occurring in three families, in one of which the parents were first cousins, are reported and the literature dealing with similar cases is briefly reviewed.

Measurement of the urinary oxalate excretion, which is always raised, is essential to distinguish these patients from other cases of juvenile urolithiasis which do not carry such a grave prognosis.

The precise level of the urinary oxalate in individual cases cannot be correlated with the apparent age at which stone formation begins or with its rate of progression. A marked diminution in the urinary oxalate excretion characterizes the terminal uraemic phase of the disease which may or may not follow a period of chronic renal failure.

Microscopic examination of aspirated sternal bone marrow and slit-lamp examination of the eyes for evidence of oxalate deposits have not been helpful in assessing the prognosis of individual cases and have given no indication of the development of oxalosis (disseminated extra-renal oxalate deposits). It is suggested, on the basis of indirect evidence, that this occurs only late in the evolution of the disease.

There appears to be no way of preventing the formation of calculi and the management of these patients conforms to the surgical practice in other cases of recurrent urolithiasis, the cause for which cannot be removed.

Hyperuricaemia was not encountered in these cases.

The familial incidence of the disease is compatible with its being due to the operation of a rare recessive genetic character.

We are indebted to the following surgeons for allowing us to investigate patients who were under their care: Mr. P. P. Rickham (Families 4 and 6) and Miss I. Forshall (Family 5). We are also pleased to acknowledge the help which we have received from Mr. J. T. Ireland and Mr. L. Rawlings.

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BOOK REVIEWS

Les Myocardites Aiguës Primitives de l'Enfant et les Virus Cocksackie. By BERNARD GRENIER. (Pp. 148. Fr. fr. 1,200.) Paris: Masson et Cie. 1959.

This monograph presents a review of recent work on the aetiology of acute primary myocarditis.

In the first chapter the author discusses some of the clinical and pathological aspects of this form of acute interstitial myocarditis, frequently called Fiedler's myocarditis, together with a discussion on points of differential diagnosis. In the second chapter the author discusses the viral aetiology at some length. Two main groups of viruses are associated with myocardial involvement—acute infectious fevers, mumps, influenza, acute respiratory disease, rubella, hepatitis and certain other viruses, herpes, vaccinia and poliomyelitis. The main substance of the monograph is devoted to an analysis of the rapidly accumulating evidence on the causal role of Cocksackie virus in acute primary myocarditis. This review shows that since Gear and others in South Africa reported on two epidemics of acute myocarditis in the newborn from which Cocksackie virus was isolated similar reports have been received from many other areas of the world. There now seems little doubt that Cocksackie virus B, and in particular serological types B2, 3 and 4, play a definite role in the causation of this disease. Having worked with Dr. J. Enders, the author has recognized the need for careful laboratory investigations in research into conditions of this nature, and the monograph concludes with a useful summary of the material needed and tests to be undertaken in such investigations.

The monograph contains a lot of useful information in a compact volume of 148 pages. There is a comprehensive bibliography.

Maladies Héréditaires du Métabolisme chez l'Enfant. By M. Lamy, P. Royer and J. Frézal. (Pp. 259; 72 figs. Fr. fr. 3,600) Paris: Masson et Cie. 1959.

It is difficult to praise this book too highly. The three authors cover a field of medicine, our knowledge of which is in a stage of rapid advance. It is also a specialized and difficult field, comprising a number of somewhat rare or very rare diseases of which the aetiology in almost every instance is quite different. The chapter headings are formidable. They leave the reader in no doubt that here is no manual for the doctor looking for a guide to children's diseases in everyday practice. A chapter on principles of genetics and the metabolic disorders is followed by those on conditions long recognized as disorders of internal metabolism and by others on conditions such as congenital hyperplasia of the adrenals less obviously included in the title.

The writing is admirably clear, concise and understandable. The language barrier need hardly cause any

difficulty to anyone with the most elementary French vocabulary, such is the ability of the authors to make their subjects seem almost simple and to express their meanings in sentences which should be an example to writers in English.

Each subject is broken up into sections which fully cover the clinical, pathological and genetic aspects. There are many illustrations, histological, radiological and clinical of reasonably good quality.

It is refreshing to find, too, that either because of European interest in this field, or because the authors have taken the trouble to read the European literature, the references they give are very largely from this side of the Atlantic. Each chapter is very fully documented.

It is to be hoped that Professor Lamy's book will find its way into most paediatric libraries.

La Coqueluche. Séminaire organisé par le Centre International de l'Enfance. (Pp. 232; illustrated; Fr. fr. 1,400) Paris: Masson et Cie.

The International Children's Centre is to be commended for providing us with such a rich source of information on whooping cough. It is the report of an international seminar with representatives from 18 countries (although the participants were predominantly French), when the diagnostic, immunological and therapeutic aspects of pertussis were discussed. Much of the original work here reported has already seen the light of day in medical journals such as that of E. K. Anderson of Denmark and D. G. Evans of Great Britain, but there is a lot that is quite new. For the paediatrician and the specialist in infectious fevers the relatively small section on treatment should hold special interest. In spite of the many new treatments tried and the claims made for them, the cure for pertussis remains yet to be discovered. The clinical and laboratory research worker will find a great deal of current research work conveniently collected together in this volume. The lack of an index or a bibliographical list is to be regretted.

Healthier Babies—Happier Parents. By HENRY K. SILVER, C. HENRY KEMPE and RUTH S. KEMPE. (Pp. 244; illustrated. 8s. 6d.) London and Glasgow: Collins.

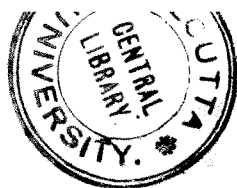
This book is so truly American that, though the publishers claim that it has been trimmed for the English market, nothing can disguise its origins. Equally divided into two parts, the first is a straightforward and comprehensive manual on child care which, it is claimed, 'can be read with profit before the baby arrives and should be regularly referred to thereafter': this claim is not idle. It could indeed profitably be read by nurses

up for the Children's Certificate Examination, and they would pass—easily. It is really remarkable how sensibly informative this section is. From line 1 'A baby does not look his best just after he is born—as everybody knows' to the last words in the book 'Happy second year and each succeeding one!', the pages turn with an easy swing; the mother is both informed and comforted through almost every possible eventuality. Throughout, the dominating note is one of quiet reassurance, and one is left with the impression, that, provided the mother reads the book carefully and, of course, turns to her own doctor with any remaining doubts or difficulties, nothing can ever go wrong. Even tetanus 'is always a serious condition and total recovery may not occur for several weeks. However, once improvement has begun the eventual recovery is complete.' Information is given over a very wide field. There are 15 points to write down for a baby-sitter, the last of which being whether she will be taken home (though it does not say at what time!); it offers four different feeding schedules 'strict timetable', 'strict self-demand' and a 'modified self-demand', alternatively called 'flexible timetable'; there is a section on a dozen or more illnesses couched in straight medical textbook style, with signs, symptoms, complications and treatment; there is advice on making up the feed by two alternate techniques, standard cleaning technique or the terminal sterilization method; and there is this statement on breast and artificial feeding: 'Breast and bottle feeding are both perfectly satisfactory ways of feeding your baby. Although breast feeding is the natural way in which to feed a baby, the majority of babies in western countries are fed by bottle, and there is every reason to believe that both methods are equally successful in satisfying a baby's physical and psychological needs.' There it is, the simple truth put forward by two well-known Professors of Paediatrics and a specialist in the field of mental health and child guidance. It is probably true, although it is doubtful whether any paediatrician on this side of the Atlantic has ever said or even thought it with such simple conviction.

Section 2 is in the form of mothers' questions, 683 of them, designed to fill up any gap that may have been left in the mother's knowledge. Each question is answered carefully and sensibly, and one is left with a feeling of admiration for the endless patience exercised by American doctors in relation to their patients. What English mother would worry (in four questions) about her baby's shoes during the eighth month, and who, in this country, would be able to explain the intricate pros and cons of high uppers for a baby of this age. Then again, who would ask her paediatrician whether at 11 months her baby is capable of developing artistic tastes, to be told sensibly 'Yes, he is, in a rudimentary way' and 'the

baby will enjoy pictures and music quite naturally if they are simple enough for him and therefore not boring'. A good example of the merits and also at times the tedious nature of the question and answer method is the following passage concerning overweight. Question 574: 'How much weight does a baby gain during the ninth month?'. Answer: 'Half an ounce a day or about a pound during the month.' Question 575: 'Should I be concerned if my baby seems overweight?' Answer: 'Usually not' with a further 12 lines of explanation. However, the mother persists—Question 576: 'Is baby likely to be healthier if he weighs more than the average?' Answer: 'No, not really' and four more lines of explanation. Question 577: 'Does a baby inherit his tendency to be overweight?' A guarded answer follows: 'A baby can inherit a tendency to gain weight easily, but this doesn't mean he has to be fat' and seven more lines of explanation. Still she persists—Question 578: 'Is it possible for a baby to become overweight even though he does not eat too much?' The answer is judicious, but one detects a tinge of exasperation: 'This depends on what you mean by "too much" . . . If a baby gets much overweight he is almost certainly eating too much.' Finally, Question 579: 'Should anything be done if my baby is overweight?' And the answer is worth quoting in full: 'Don't do anything without asking your own doctor. Usually a mild degree of plumpness in babies does absolutely no harm at all. Let your doctor decide whether your baby is too plump. If he feels your baby should lose weight he will give careful instructions about diet. Never put your baby on a special diet without asking your doctor. You might be leaving out foods which are important.' This quaint conversation is perhaps a little hard on the book since many of the sequences are intelligently planned to give valuable information on important subjects, but it does illustrate how these mothers, though copiously primed with detailed information on baby care and quasi-medical knowledge, lean on their family doctors and paediatricians, and how careful the authors are to encourage this attitude.

The illustrations, profusely scattered throughout the pages, are not more than thumbnail sketches of a pixy-like triteness, quite unworthy of the highly informative and serious tone of the book which really only lacks a little of the boisterous fun and self-confidence of Spock's paper-back, which sold for 5s. across the counter of chemists' shops and has since been translated into many languages including Russian. The present handsomely bound book, which could in this country undoubtedly be useful to the middle-class counterparts of the American mother, will surely not appear in Russian or English chemists' shops except perhaps in Bond Street.



FORTY YEARS OF NEPHROSIS IN CHILDHOOD*

BY

DAVID LAWSON, ALAN MONCRIEFF and WILFRID W. PAYNE

From The Hospital for Sick Children, Great Ormond Street, and the Institute of Child Health, London

(RECEIVED FOR PUBLICATION JUNE 19, 1959)

This article is an attempt to relate the present-day outlook on nephrosis in childhood with the 'natural history' of the disorder as it was seen at The Hospital for Sick Children, Great Ormond Street, in the days before modern treatment was available. The first period of the study is the responsibility of one of us (D.L.) and covers the years 1917-38. During the war years in-patient care of the children attending this hospital was widely dispersed and records are not always available. With the opening up of the hospital to more than a handful of patients in 1945 and the development of a new index system the study starts again and covers up to 1956-7. This period falls into two parts: for 1945-51 it had become possible to prevent and treat infection in children with nephrosis by means of sulphonamides and antibiotics; from 1951 steroids became available, at first in limited supply for selected cases, and in 1955 freely available for all cases as required.

The Hospital for Sick Children, Great Ormond Street has a large turn-over of patients and serves a wide area. This means that large numbers of case records have to be read and details checked before a child can be accepted as qualifying for inclusion in the series. It also means that follow-up of children, especially after they have passed the age for attendance at the hospital, presents many difficulties.

Definitions

For the purpose of this study the term nephrosis is applied to a syndrome presenting four essential characteristics, namely oedema, gross proteinuria, lowered plasma albumin and raised blood cholesterol.

The disorder presents, usually in the absence of any constitutional disturbance or other symptomatology, with the unheralded onset of generalized oedema. In severe cases the child becomes universally waterlogged in the course of a few days,

although a slower but steady increase in oedema over the course of two or three weeks is commoner. The urine, which has usually been unremarkable in quality, although often moderately diminished in quantity, is found to contain from 500 to 2,000 mg. % of protein but only a moderately increased red cell content. Addis counts of up to 10 million are not uncommon but the haematuria seldom amounts to more than this and is almost never macroscopic. The serum cholesterol is usually raised at the 'onset' but, if not, it steadily rises in the course of a few weeks to levels between 400 and 2,000 mg. %. The plasma albumin concentration is always markedly decreased and may be below 1%.

An infection often precedes the clinical onset but it is seldom clearly streptococcal and is more often in the nature of a common cold or bronchitis. Subsequently, it is often found that such infections will precipitate a return of, or an increase in the degree of, oedema and it is easy to understand that such an episode may first bring the hitherto sub-clinical disorder to light. The oedema may last for a few weeks only or may persist over months or years with alternating remission and relapse. When onset or relapse can be closely studied biochemically, it is found that the oedema is the last of the signs to appear in relapse and the first to disappear in remission, with the possible exception of proteinuria. After such a variable course all the manifestations may clear and the disorder may appear to be healed. Death may occur in periods of severe oedema from biochemical and water-balance disturbances or from overwhelming bacterial infection to which these children are particularly subject; or there may be a gradual or rapid superimposition, at any phase, of the features of generalized renal failure and hypertension with final death in uraemia. The transient occurrence of nitrogen retention or hypertension, particularly common in periods of increasing oedema, does not however itself presage such a termination.

In the 1945-57 series clinical notes and biochemical

* A summary of this paper was given at the IX International Paediatric Congress, Montreal, in July, 1959.

records have been fairly complete; most of the cases could be followed up and re-examined and all were within the memory of authors or colleagues.

The extraction and definition of the 1917-38 series was more difficult because (1) records, and in particular biochemical investigations, were less complete; (2) there were no existing follow-up studies as out-patient records for the period did not survive the Second World War; and (3) the unity of this disease was not recognized at the time and cases were found under a wide range of diagnostic headings. Biochemical criteria were applied wherever possible, but in many cases a subjective element had to be introduced.

When the question of differentiation between nephrosis and acute glomerulo-nephritis arose, main reliance was placed on the following contrasting features in the natural history of acute glomerulo-nephritis: (1) sudden onset with urinary signs, often within 10-14 days of a streptococcal infection; (2) transient nature of the oedema; (3) rapid rise and fall in any transient initial nitrogen retention and hypertension; and (4) normal blood cholesterol and plasma protein at clinical onset.

Classification

For the purpose of analysis the cases have been placed in one of the four following groups:

Inactive. This means the absence of the four essential criteria already quoted. Albuminuria must not exceed 50 mg. per 100 ml. The electrophoretic pattern of the plasma proteins is normal.

Latent. There is no oedema but albuminuria is above 50 mg. per 100 ml. and blood urea and cholesterol levels may or may not be normal.

Active. This group consists of cases with the complete, potentially reversible nephrotic syndrome just described, who may have transient increases in their blood urea and blood pressure, and also cases who have progressed to the irreversible uraemic stage, as judged by a persistently high and increasing blood urea and an increasing blood pressure.

Dead. The cause may not always be directly related to the nephrosis.

The second group is the most controversial and must be further discussed. By oedema in a follow-up series is meant essentially the pre-tibial oedema of the child, otherwise apparently well, who is attending the out-patient department, not the water-logged condition of the in-patient which fluctuates so much and not always for obvious reasons. There is no simple way of screening patients other than by looking for the pre-tibial oedema. All such cases will have some degree of albuminuria. When the oedema goes the child is clinically normal, but there

may or may not be albuminuria of over 50 mg. per 100 ml. If there is no such albuminuria then the child will almost certainly come into the inactive group provided that the blood chemistry is normal. Strictly speaking therefore inactive means clinically normal (i.e. no oedema) and chemically normal. The latent group seems to contain three subdivisions: (a) clinically normal but still albuminuria of over 50 mg. per 100 ml.; (b) clinically normal but both albuminuria and abnormal chemistry; and (c) clinically normal, no albuminuria but blood chemistry not quite normal. It is recognized that this latent stage may persist, but it only appears in a very small number of the patients whose records have been analysed in the 1945-57 series and the transfer of such patients to either the inactive or active groups will not affect the main conclusions.

Description of Search (1917-38 Series)

The in-patient case records for this period are bound in volumes at the end of which is a diagnostic index prepared by the registrar. All these indices were searched and every case history examined in which there appeared the remotest possibility that it might be a case of nephrosis. These diagnostic terms included every case in which the word nephritis of any kind was used and any in which the words oedema or toxic oedema were used. This resulted in a close study of the records of 1,500 cases. The greatest care was taken to make this selection as accurate as possible, but in certain cases recourse had to be made to something closer to intuition than to scientific study in view of the paucity of records. The author (D.L.) who carried out this part of the work is however satisfied that the diagnosis was almost certainly correct in every case included and any doubtful ones were discarded.

Analysis. The total number of cases found in this way was 78. Of these 18 had died during the first or subsequent admission and 60 had been discharged and lost from the records (Table 1).

TABLE 1
SEARCH AND FOLLOW-UP (1917-38 SERIES)

In-patients' Records Searched		1,500
Accepted as nephrosis		78
Died in hospital		18
Follow-up attempted 1953		60
Follow-up failed 1953		44
Followed up 1953		16

An attempt was made in 1953 to trace these 60 cases. Letters were sent to them at the recorded addresses and if no reply was received a further letter was sent. In a number of cases the patients could be traced at these addresses and in others

information was given by the present occupier which led to their successful tracing subsequently. This search was completely unsuccessful in 44 of the 60 cases. Sixteen were successfully traced and of these five had died (Table 2).

TABLE 2
ANALYSIS OF 16 CASES SUCCESSFULLY FOLLOWED UP IN
1953 (1917-38 SERIES)

Died	5
Alive and well	11
Active	0
Latent	1
Inactive	8
Unclassified	2 (in perfect health but not examined)

The remaining 11 were asked to come to the out-patient department for clinical and biochemical examination and nine did so. None of these had had any clinical relapse since his admission to hospital in childhood. All were in perfect health and none showed any clinical or biochemical evidence of activity or of sequelae of any kind, except for one woman who had borne children without mishap but whose urine contained 100 mg. % of protein. This technically places her in the latent rather than the inactive group. The remaining two were unable to come but sufficient information could be obtained to ensure that they were in perfect health.

Causes of Death (1917-38 Series). The 23 known deaths in this series have been classified as follows (see Table 3):

TABLE 3
ANALYSIS OF CAUSES OF DEATH (1917-38 SERIES)

	No. of Cases
Bacterial infection	9 (includes 1 measles)
Treatment	5
Uraemia	4
Water and electrolyte disturbance (includes D. and V.)	3
Diphtheria	1
Unknown	1
Total	23

(1) INFECTION (nine cases). In all cases this was a bacterial infection with the exception of one child who died in a severe attack of measles. In the majority of cases the infection took the form of cellulitis, peritonitis and pneumonia, often accompanied by a septicaemia. There have been excluded from this heading infections which were the direct result of treatment.

(2) DISTURBANCES OF WATER AND ELECTROLYTE BALANCE (three cases). This includes children who died from overwhelming oedema and also those in

whom the cause of death was given as 'gastro-enteritis'.

(3) URAEMIA (four cases). Children who died in chronic uraemia with or without hypertension.

(4) DEATH DUE TO TREATMENT (five cases). This includes two children who died suddenly following over-rapid paracentesis, one who died of post-operative pneumonia following a renal biopsy, one who died with convulsions without previous nitrogen retention in the post-operative period following a decapsulation operation, and one who died following decapsulation, paracentesis and subsequent wound infection.

(5) UNCLASSIFIED (two cases). One appears to have been in perfect health for some years following discharge but died of diphtheria, and one died after discharge but the cause of death is unknown.

Of 21 cases in which the cause of death is known, therefore, all but four are deaths which could probably have been avoided had modern techniques of fluid and electrolyte balance and modern chemotherapeutic agents been available, and if methods now known to be useless and dangerous had not been used.

Estimate of Mortality (1917-38 Series). Of the total of 78 cases 18, or 23%, died during an initial or subsequent admission to The Hospital for Sick Children. In view of the incompleteness of the follow-up it is not possible to make a very accurate assessment of the subsequent mortality of the cases who were discharged alive. The first question to be answered is whether or not it is reasonable to assume that the 16 cases who could be traced were a representative sample of the 60 in which the attempt was made. This turns on the question of whether it is likely to be more difficult to trace patients who have died than to trace those who have survived.

TABLE 4
ROUGH ESTIMATE OF MORTALITY (1917-38 SERIES)

No. in series	78
Deaths in hospital	18
Deaths after discharge 5 out of 16, equivalent to to 19 out of 60	19
Mortality approximately 37 out of 78=47%	

It is in fact the families rather than the individual patients who are being traced, and there seems no reason to think that it would be more difficult to trace the family of a child who had died than of one who had survived, although it is possible that the families of children who have died might be less willing to reply if they received the letter. Of the 44 untraceable cases, in all but four the follow-up letters were returned by the Post Office marked 'Not known at this address'. There were only four cases

in which letters were not so returned by the Post Office and had therefore presumably been accepted at the address given. In these circumstances it is considered reasonable to assume that the 16 cases traced may be regarded as a representative sample of the 60 and the approximate overall mortality of the series is as follows: Five of the 16 are dead; therefore of the total of 60 it may be assumed that 19 are dead. To these 19 presumed dead must be added the 18 who are known to have died while in hospital, giving an overall mortality of 37/78 or approximately 47% (Table 4).

It therefore appears that in the years 1917-38, before the days of antibiotics and steroids, the recovery rate was of the order of 50% and that of 21 cases in which the cause of death is known all but four (or approximately 20%) were due to causes which might have been averted by modern methods of control of infection and water balance disturbance.

Description of Search and Analysis (1945-57 Series)

For this period of the study indexed diagnoses and a special list held by one of us (W.W.P.) were accepted in the first instance, and during the 12 years or so covered the number of children classified as nephrosis was 123. Of these, five were private patients under the care of colleagues, and for various reasons records were not always complete nor was follow-up easy to arrange. They have therefore been omitted. Some of the remainder were seen as out-patients and transferred to other hospitals at once or after a short period. Their records have been used only in regard to age of onset and ultimate fate, if known. One of us (A.M.) read all the case records and reduced the data to a single *pro forma* sheet. This proved a fascinating but formidable task. Patients were often in hospital for long periods or were admitted on several occasions. (The record was held by one child admitted 23 times.) When no recent information existed this was obtained by seeing the child, by writing to the family doctor, to another hospital and so forth. As already mentioned, patients come to the hospital from a wide area and the tracing of them after discharge has been extremely difficult.* Altogether

* It may be mentioned in passing that successes in tracing included details obtained and contacts re-established in numerous ways. The police traced the address of one family; another patient was found after an announcement of her marriage engagement in *The Times*; the trail of one began in Wales, followed to a wrong part of East Africa, eventually finished in Central Africa and the child was seen in Out-patients when the father was next on leave. (She had actually made an apparently complete recovery which early records would not have suggested.) The Service authorities have been most helpful in tracing patients overseas, one going as far as Singapore. In other areas the health authorities have been most helpful and family doctors most willing to assist. One child in Malta, who was an in-patient, has been reported on whenever necessary.

failure has to be recorded for four children in the 1945-57 series. One is the child of a United States Air Force officer who has returned to the U.S.A. and, despite every possible effort on the part of the authorities, the present whereabouts are unknown. Three others were all going downhill shortly after the end of the war and cannot now be traced. Two of these were in fact rejected on further study of the records and are included in the 12 rejects to be mentioned later. Therefore of the true nephrotics in the series only two have been lost. After deducting lost patients, exclusions and transfers, there are 102 left for the purpose of estimating gross results and other factors (Table 5).

TABLE 5
PERIOD 1945-57

Case records abstracted	123
Selected in error	1
	122
Private patients	5
	117
Excluded on further scrutiny	12 (2 not traced)
	105
Transfer and no follow-up	1
	104
Not traced	2
	102

As already pointed out, this period can be divided into two main sections. Up to 1951 chemotherapy was available and then steroids were introduced, at first (since the supply was short) for limited and selected cases and by 1955 for all considered suitable. Detailed analysis as regards treatment will be given later. Here the gross results are considered according to the definitions already set out. In the 102 children successfully followed the disorder is considered to be inactive in 49, latent in nine and active in six. The remaining 38 are dead. This gives a crude recovery rate of about 50% or the same as in the 1917-38 series when neither chemotherapy nor steroids were available. There is however a strong suggestion, supported by a small number of cases, that maintenance methods of using steroids have remarkably altered the picture.

A histogram (Fig. 1) illustrates the distribution on the basis of age at onset of the oedema, showing the usually accepted peak between 1 and 5 years of age. The deaths are very much the same proportionately for each age group throughout the series. The three children with a recorded onset before 6 months of age are the subject of a special note on congenital nephrosis on page 125.

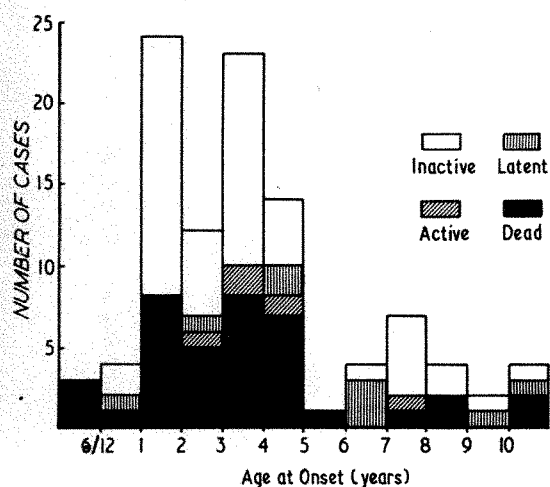


FIG. 1.—Histogram showing age at onset in 102 cases of nephrosis (1946-57 series).

The totals for the whole series are shown in Table 6. This shows a higher incidence in boys and a slightly higher mortality rate among boys than

TABLE 6
GROSS RESULTS (1945-57 SERIES)

	Total	Boys	Girls
Cases followed	102	59	43
Inactive	49	25	24
Latent	9	6	3
Active	6	5	1
Dead	38	23	15

girls. The numbers for latent or active cases are, as already mentioned, small in relation to the clear-cut groups of a satisfactory or fatal ending.

Table 7 gives details of the records of 12 patients in the 1945-57 series which, on final scrutiny, have not been included in the total of examples of nephrosis. Reasons for the rejection are given in the final column. The other columns indicate why at first sight the records appeared to justify inclusion. Since over half are known to be dead, and most of the others to be going down-hill, it seemed important to remove them from the series, otherwise they would have erroneously weighted the dead, active or latent groups.

TABLE 7
NEPHROSIS RECORDS REJECTED ON FINAL SCRUTINY (1945-57)

Name	When First Seen					Reasons for Rejection
	Age (yr.)	Oedema	Urinary Proteins (mg. %)	Total Serum Proteins (mg. %)	Blood Cholesterol (mg. %)	
Kenneth B. ..	12	Nil	440	4.7	Not done	No oedema; persistent haematuria; probably chr. nephritis
Margaret D. ..	2½	+++	1,500	3.6	870	Raised blood urea; haematuria type 2 nephritis from onset; acute nephritis 8 mth. before
Raymond E. ..	7½	+++	700	3.3	470	Haematuria ++; scarlet fever 3 yr. before; chronic nephritis
Daniel H. ..	8	Minimal	700	5.62	208	Hypertension; hepato-splenomegaly; chronic nephritis
Peter H. ..	10	++	Nil	3.02	367	Never any albuminuria at G.O.S.; ? 'cured' before admission; oedema for 7 weeks at age 4½ yr.; lost to follow-up
Michael H. ..	3½	+	140	4.49	386	Latent stage when first seen; died chronic nephritis age 10 yr.
Michael K. ..	1¾	+++	Gross	3.62	394	Transferred
Peter L. ..	1	Nil	800	4.6	356	No oedema at any time; persistent red cells in urine
Vera M. ..	9	Slight	800	4.4	—	Lost in follow-up; raised blood pressure; acute nephritis aged 9 yr.
Lothan M. ..	9	Nil	1,000	5.6	—	No oedema; blood urea 148 mg. %; died chronic nephritis
Christopher S.	4	Nil	375	5.9	166	No oedema at first attendance; latent in 1951
Julian S. ..	6½	Slight	400	5.3	206	Fibrocystic disease; cirrhosis of liver; died aged 7½ yr.

Results of Treatment (1945-57 Series)

In the 1945-57 period a low salt and high protein diet was almost universally the basic treatment for cases of nephrosis while in hospital. Sometimes a diet which was almost salt-free was given, but sometimes it was found to produce abnormally low levels of serum sodium while oedema still persisted, and it is now rarely used. As well as this basic diet, various other forms of treatment were tried.

Thyroid. It was for a long time considered that thyroid had a place in the treatment of nephrosis and many cases were given this substance. Some cases were given thyroid up to the level of tolerance, shown usually by the onset of diarrhoea. In others normal therapeutic doses only were given ($\frac{1}{2}$ -1 gr. thyroid daily).

Resins. With the introduction of resins, in a form suitable for therapeutic use, a group of children was treated using various types of resin. The results have been published in more detail elsewhere (Payne and Wilkinson, 1951).

Diuretics. Several types of diuretic have been used.

UREA. When urea is used as a diuretic it has been found necessary to give relatively large doses, such as 15 g. a day, and at the same time to restrict the fluid intake. Until the blood urea reaches approximately 100 mg.%, diuresis does not occur. When this level is reached diuresis follows in some cases. In others, unfortunately, no diuresis occurs. Increasing the blood urea to a higher level almost invariably produces such severe discomfort that it is impractical as a form of treatment. The misery of the child in these circumstances is most striking. When successful, the treatment can be maintained for many months.

WATER. Diuresis will result from forced water intake. Again this is by no means always possible. In some cases there is an initial retention of water and then any excess water given is excreted quantitatively. In other cases the excess water carries with it some of the oedema and a genuine diuresis occurs with loss of oedema.

MERCURIAL DIURETICS. Mersalyl was the most frequently used and, as with other diuretics, there was sometimes an initial diuresis which in general was not maintained with further doses.

NON-MERCURIAL DIURETICS. Usually these have had no effect but occasional diuresis has occurred with the first few doses. Subsequent doses have proved ineffective.

Fever. In a few cases production of fever, either by measles or malaria, has been used, but the

numbers are too small for use in this study. Usually there has been an initial loss of oedema followed in almost all cases by a return of oedema at varying intervals of time.

In Table 8 the results of individual treatments are shown, the results being classified as inactive, latent or active, according to the child's condition at the end of any particular period of treatment. The majority were on a basic low-salt high-protein diet and antibiotic treatment when necessary. Examination of this Table will, of course, show many more case treatments than the actual number of children. It will be seen that the number of cases classified as inactive occur mainly in the group which had rather prolonged treatment on the basic diet alone.

In two of the 36 treatments with urea the inactive state was reached, but the other diuretics, resin or water, produced only a transient improvement: five of 14 cases treated with water and 10 of 36 cases treated with urea became latent. Of the 23 cases receiving the basic treatment plus thyroid, five became inactive and six latent, and of the 49 case treatments in which no specific treatment other than the basic diet was given, 16 became inactive and 13 latent.

TABLE 8
RESULTS OF TREATMENT (1945-57 SERIES)

Treatment	Number	Result		
		Active	Latent	Inactive
Basic alone	49	20	13	16
.. + thyroid	23	12	6	5
.. + resins	13	12	1	0
.. + urea	36	24	10	2
.. + water	14	9	5	0
.. + other diuretics	19	18	1	0
None	—	—	—	10

It will thus be seen that no better results were obtained when any specific treatment was given than when basic treatment alone was given. In fact, since the duration of the basic treatment was normally much longer than that of the specific treatment, the results appear much better.

The total number of cases not receiving steroids and becoming inactive in this group was 33: 10 recovered after being discharged and were presumably on no particular treatment at all.

Steroids. These became available in small amounts in 1951. A few cases were treated in the first years, and subsequently the use of steroids as the main treatment became general. Since 1951 the way in which steroids have been used has changed considerably and, largely owing to the more critical examination of results, the general aim of individual treatment has altered. Before steroid treatment

there was no known method whereby the albuminuria could be controlled, and most clinicians planned the treatment of their cases on the basis of getting rid of the oedema and hoped that the albuminuria and other abnormalities would clear up in time, but the disappearance of the oedema was regarded as the therapeutic aim. (This point is discussed at greater length later.) It was on the disappearance and re-appearance of oedema that the reputation for frequency of spontaneous remissions and relapses in nephrosis was based. If the stricter criteria for apparent recovery are used, it will be seen that, although there is still a liability to relapse, it is by no means as frequent as was previously considered.

The records have been examined using these stricter criteria and, of the 15 children who reached the inactive phase and had had steroid treatment, two cases only relapsed, one recovered spontaneously and the other recovered after further treatment. In 22 cases of children not receiving steroids, who reached the inactive stage, only one case relapsed, and that case also made a spontaneous recovery. However, in the steroid-treated cases who have reached the inactive stage relatively recently, intercurrent infections may cause a transient return of the albuminuria, lasting from a few days to two or three weeks and disappearing without treatment.

Initially, short courses of steroids were given, either ACTH or cortisone. ACTH was usually given for eight to 10 days in varying doses, usually 20 to 40 mg. daily, and cortisone in doses from 100 to 200 mg. daily for approximately 10 days. In both cases at the end of that period treatment was abruptly stopped. This was called the short treatment. In most cases diuresis occurred and generally oedema disappeared but albuminuria, although frequently lessened, was generally still present and in most cases the oedema returned later on.

The next phase was to give larger doses, 200 to 300 mg. of cortisone, or the equivalent of prednisolone, or if ACTH was used, 80 mg. daily using the gel in divided doses. This treatment was maintained for approximately one month and then the steroids were tailed off fairly quickly, usually within two to three weeks. This type of treatment has been called long-term. In general in these cases the albuminuria disappeared only to reappear as the dose was being tailed off or very shortly afterwards.

In the next form of treatment, called maintenance treatment, steroid therapy has been maintained at a slowly decreasing level for much longer periods. There is much difference of opinion as to the ideal way of doing this. In the majority of the maintenance cases an initial month's treatment is given

similar to that in the long-term, by which time there is usually no albuminuria and the plasma proteins are approaching normal while the cholesterol is falling. The dose is then cautiously reduced by 10 to 15% every week at first and later every fortnight. This slow reduction is continued as long as there is no albuminuria. Usually within two to three months the plasma proteins are chemically and electrophoretically normal and the cholesterol also has returned to a normal level. If these values are slow in returning to normal the therapy is continued for a longer period and the intervals between reductions are increased. If albuminuria returns during the period of reduction, the dose of steroid is increased until it disappears again. Reduction is then carried out more slowly.

In a few cases the intermittent high dosage treatment was used, 400 mg. cortisone three days in succession, followed by four days without steroid.

In assessing the final outcome, the cases have been divided into two groups, those who have received steroids and those who have not. The results are given in Table 9. The results in this Table are

TABLE 9
RESULTS OF TREATMENT WITH STEROIDS

	No Steroids		Steroids	
	(no)	(%)	(no)	(%)
Total cases	62		40	
Inactive	33	53	16	40
Latent	5	8	4	10
Active	4	7	2	5
Dead	20	32	18	45

somewhat unexpected. It appears that the results from steroid treatment are definitely inferior to those when no steroids are given. One possible explanation for this is the inclusion in the steroid group of cases carried over from the previous group which were already doomed to failure.

Table 10 is an analysis of the deaths in the two groups. Uraemia accounted for more than half the deaths but, whereas 10 cases of uraemic death

TABLE 10
CAUSES OF DEATH

	1917-1938	1945-1957	
		No Steroids	Steroids
Uraemia	4	10	10
Heart failure	—	1	2
Infections	10	3	2
Cystinosis	—	2	—
Pulmonary embolism	—	—	2
Electrolyte imbalance	3	—	—
Treatment	5	2	2
Not known	1	2	—
Total	23	20	18

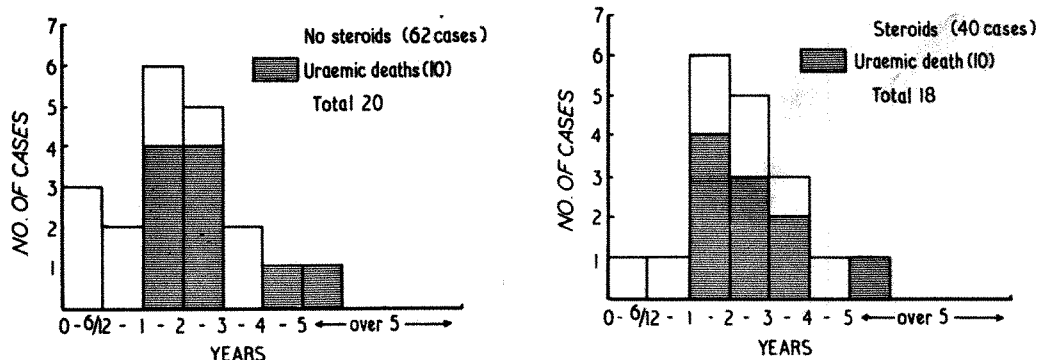


FIG. 2.—Histogram showing duration to death in 38 cases (1945-57 series).

occurred out of 62 non-steroid cases, the same number occurred in only 40 cases given steroids (Fig. 2). Although this suggests a slight increase in uraemic death, it is hardly sufficient to account for the difference in the two groups. A more detailed analysis of the effects of steroid treatment based on individual treatments using the same criteria as in Table 8 is shown in Table 11. In this Table are included cases treated in 1957-58 which were not included in the 102 cases under survey. This Table brings out the difference in ultimate results between the short, long and maintenance types of treatment, and largely explains the apparent inactivity of steroids shown in Table 9.

TABLE 11
RESULTS OF TREATMENT WITH STEROIDS

	1951-57			1957-58			
	Short	Long	Maintenance	Short	Long	Maintenance	No Treatment
Total treatments	35	36	6	3	8	4	1
Inactive	0	10	6	0	2	4	1
Latent	10	13	0	0	0	0	
Active	25	13	0	3	6	0	
'Cure' %	0	28	100	0	25	100	

The numbers treated on maintenance are not significant and the 100% cure reached is certainly accidental and is partly due to the fact that only cases whose treatment had been completed were included in this Table. In order to appreciate more fully the effect of steroid treatment a study of Table 8 (individual treatments, non-steroid) is necessary. It is apparent from this that no individual treatment produces as good results as simple dietary measures alone, or even no treatment at all. It is against this background of spontaneous remission that the results of steroid treatment should be assessed.

In Table 12A the length of time elapsed between onset of disease and cure, in the steroid and non-steroid cases, is compared, and it will be seen that steroid treatment definitely produces more rapid cure.

In Table 12B the time relationship between onset and death shows that in the fatal cases there is no material difference.

Tables 12C and D show the ultimate result and the interval of time between onset of disease and the start of steroid therapy. There is no suggestion in these Tables that better results are obtained when steroid therapy is started early.

TABLE 12

A	Time between Onset and Cure					Total
	< 6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	> 5 yr.	
No steroid	(no.) 5	(no.) 4	(no.) 4	(no.) 13	(no.) 7	33
Steroid	2	2	3	9	—	16
B	Time between Onset and Death					Total
	< 6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	> 5 yr.	
No steroid	3	2	6	8	1	20
Steroid	1	1	6	9	1	18
C	Time from Start of Steroid Therapy to Cure					Total
	< 6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	> 5 yr.	
	7	1	2	6		16
D	Interval between Onset of Disease and Steroid Therapy					Total
	< 6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	> 5 yr.	
Cure	8	2	3	3		16
Death	9	3	4	2		18
Latent or active	2	1	1	2		6

In analysing the causes of death the hazards of treatment have to be considered. In the period 1917-38 it will be observed that a fair number of deaths can be attributed directly to treatment. It is not quite so obvious in the period 1945-57 but a suspicion by one of us (A.M.) that mersalyl was a dangerous treatment has been confirmed. The results in 12 cases treated with mersalyl are: inactive (1), latent (1), dead (10). These results strongly suggest that mersalyl in itself is dangerous. That it was used merely as a last resort was not found to be the case on examining the notes, since in most cases it was given in the first 12 months from the onset of disease.

It must be realized that steroid treatment is potentially dangerous and the group of cases we have treated shows the following results:

Died of overwhelming infection	1
Sudden cardiac failure and death on the fourth day of cortisone treatment	1
Decalcification of vertebrae	1
Acute cerebral crisis with unconsciousness and fits (? cerebral oedema), with ultimate recovery	1
Adrenal crisis, low blood pressure, low serum sodium and collapse	2

Thus, of the 18 steroid deaths, two can be attributed to steroid therapy, and both the cases of adrenal crisis could quite well have been fatal if they had not fortunately occurred while in hospital.

Discussion

The literature on nephrosis threatens to become unmanageable. This paper is essentially concerned with a presentation of facts as ascertained from a study of the disorder in childhood in hospital records for over 40 years. It is not proposed to discuss the pathology or pathogenesis. The definitions already set out indicate what sort of disease process is being considered. The results of treatment, with special reference to those obtained by the use of steroids, can usefully be compared with those presented by McCrory and Fleisher (1958), Metcalf (1958) and Riley and Scaglioni (1959). A useful historical survey was given by Mann (1958) on the occasion of the Bright centenary celebrations.

If the assumptions made in the section which considers the 1917-38 series are accepted as correct, then about half the patients are dead. In the 1945-57 series as a whole about half are either dead or in an active or latent phase. Some of those classified in the last two categories at the time of assessment may by now have moved or will move into the inactive group, so that broadly speaking these results probably show a slight improvement over the results of 1917-38, but certainly not as great an

improvement as might have been expected with the better control of infection and, in the later cases, an active agent to attack what is probably the fundamental lesion which leads to the proteinuria. Again, if the 1945-57 group is broken down into those who did not receive steroids and those who did, there is no dramatic improvement with the new drugs, at any rate in the early years before the best method of using steroids was worked out. Indeed, taking the overall figures as shown in Table 9, there is a 45% mortality rate in the steroid-treated cases compared with only 32% in those not receiving steroids, with 15% in each group still classified as latent or active.

A review of the causes of death in each of the three periods shows that 17% died of uraemia in the pre-antibiotic era, the remainder dying from causes such as infections, which now would be regarded as curable. Since the introduction of antibiotics the cause of death has changed and is now uraemia in over 50% of cases (Table 10).

However, deaths which would have been theoretically preventable still occur and in the final analysis uraemia and heart failure seem to be the expected causes of death in nephrotic children. A small unknown proportion of these uraemic deaths will be due to unavoidable errors in initial diagnosis, such as in those cases shown in Table 7, which were retrospectively rediagnosed. Until more certain means of diagnosis are utilized (such as renal biopsy), this error will prevent an accurate prognosis, and therefore a proper evaluation of treatment, being made. From studies already published (Vernier, Farquhar, Brunson and Good, 1958) it is likely that in the majority of cases the correct diagnosis can be made in the early stages of the disease. Thus, a death rate from uraemia and heart failure of 23% of all recent cases (and it will become higher, since many of the still active cases are already uraemic) indicates that a proportion of 'pure nephrotic' children will die of uraemia. A small proportion will still die of intercurrent accidents, preventable or not; the remainder, if they can be kept alive, should recover. It is impossible to assess this figure accurately, but it is over 50% and probably about 60-70%, as judged by the non-uraemic causes of death. Any treatment must have a 'cure' rate of about 80-90% before it can be regarded as of real value. Table 12 shows that the majority of deaths occur within the first five years of the disease, so it should be possible to determine if a given treatment has successfully prevented the development of uraemia when enough cases have been treated for over five years. At the present moment the evidence is only sufficient to indicate a promising trend.

In considering the value of many of the remedies used, the aim of the treatment at the time must be borne in mind. Until quite recently the physician's primary aim was the cure of the oedema, with the hope that in due course the remaining pathological changes would cure themselves. With such an imperfect criterion of cure it is not surprising that relapses were many and frequent. Thus, when examining Table 8, all the latent results would have been called cures. Even with this proviso, it will be seen that the more common methods of therapy were quite ineffective when compared with the basic treatment (low-salt, raised-protein diet). In a small series of eight cases treated with measles and two with malaria, seven reached the latent stage, but only one became inactive without further relapses.

Since the oedema most frequently causes the patient to consult a doctor, its disappearance must have a good effect on the outlook of the child and his parents, although there is no direct evidence that removing oedema improves the prognosis. Thus it is reasonable to take non-specific measures which will help in its removal, providing that they are harmless. For example, urea, resins, water and occasionally non-mercurial diuretics are useful. For the same reason a low-salt diet is given.

Oedema, if severe, can be very distressing and can even endanger life. In these cases acupuncture of the dependant legs and abdominal paracentesis, both under antibiotic cover, have been used and occasionally a complete remission has followed.

Steroid treatment has undoubtedly made a big change in the method of treating nephrosis. In the early days, when removal of oedema was the therapeutic aim, short eight to 10 day treatments were used with an initial gratifying effect but, as with previous methods, relapses occurred, which were more resistant to further treatment with steroids. The aim of treatment was altered to complete reversal of all pathological changes. Much longer terms of treatment were used and the results began to be more encouraging. While, as yet, no uniform method has been arrived at, the general principle is to give adequate dosage of a steroid preparation, the equivalent of 240 to 300 mg. cortisone daily. It does not appear to make much difference which of the new, less sodium-retaining steroids is used. Treatment is continued for six to 12 months according to the plan for reduction already mentioned. Clinically it seems that it needs many months to reverse completely the pathological changes in the glomerular basement membrane, if indeed this can be done. Since it is probable that some 20-30% of untreated patients will progress to irreversible renal damage, the

essential fact to determine is whether in these cases it is possible to prevent this.

As has been pointed out, this can only be done when sufficient time has elapsed for such changes to develop—at least five years. This delay in making a judgment of cure is necessary since steroid therapy can remove the nephrotic symptoms for a time in cases in which the diagnosis is known not to be simple nephrosis. Until an adequate period has elapsed it is possible only to say that the latest results are promising in that a high percentage are reaching the inactive stage.

It has frequently been stated that liability to a return of nephrosis can never be eliminated. It is clear that clinical relapse is common if only the latent stage is reached. When the inactive stage is reached relapse is less frequent but may still occur. Many patients, whose nephrosis has been successfully treated with steroids, for some years tend to get transient albuminuria during fairly mild intercurrent infections. In a few this proceeds to a full relapse which may need a further course of steroids.

This raises the fundamental question of the aetiology of nephrosis. Should the condition be regarded as an inborn liability of the kidney to a special type of pathological response to certain insults, or should the pathological response be regarded as due to a specific insult, such as is believed to occur in acute nephritis following infection with certain types of streptococci? If the former view is held, it is unlikely that any form of treatment will prevent recurrence of symptoms even many years later. In the second possibility, once a cure is complete, relapse would only occur with a further specific insult. Such clinical evidence as exists suggests the former view as being possibly the more likely since occasionally relapses have recurred after many years of freedom from symptoms.

To sum up, the natural course of nephrosis, if intercurrent infections are adequately dealt with, is for at least 50% and probably nearer 60-70% of the patients to be cured, but there is also an inborn liability to relapse. There is in every series, based on clinical diagnosis alone, a small group with a different pathological basis and a bad prognosis. No treatment has yet been shown to improve the ultimate prognosis, although some treatments have worsened it. The most recent method of steroid therapy, while very promising, has undoubtedly hazards which must be balanced against the present uncertainty that permanent improvement in prognosis will occur.

Since delaying the start of steroid therapy does not seem to affect the ultimate result (Table 12D) and since a proportion of untreated cases remit

spontaneously within a few months (Table 12A), delay of up to three months in starting steroid therapy is suggested to allow time to see if there are signs of spontaneous improvement. There is no evidence that any adjuvant treatment has a material effect, apart from the need to give an adequate protein diet and to keep the salt content low when there is oedema, especially during steroid therapy. Complete bed rest, except when there is gross oedema, is not necessary. A change from prolonged bed rest to reasonable activity at The Hospital for Sick Children caused no worsening of the prognosis and a decided improvement in the children's morale. Another advantage of permitting reasonable activity is that the child can be sent home and attend school when desired while still on steroid or other therapy.

It is difficult to assess the value of the routine use of antibiotics. Oral penicillin has been used in the present series ever since it became available, reinforced by other antibiotics if an intercurrent infection occurred. This has been quite successful, and it has not been necessary to reduce steroid dosage because of infection. Prophylactic antibiotics or sulphonamides have been used to try to prevent intercurrent infections, but they have not been successful.

Note on Congenital Nephrosis

Three of the children in the 1945-57 series manifested the nephrotic syndrome at or within a few weeks of birth and all died. Two of these were siblings (boy and girl) whose parents were first cousins and they have been reported elsewhere together with a third case (not in the Great Ormond Street series) whose parents were also cousins (Giles, 1957). Briefly, the post-mortem changes were mainly in the proximal tubules, and doubly refractile crystals were present. It is likely that the whole condition was related to cystinosis.

The third child in the present series was the first child of unrelated parents who have since had a normal child. Her eyes were reported as swollen at birth and there was a sudden weight gain about the tenth day. Generalized oedema appeared at about the fourth month. She was given mersalyl at another hospital and later referred here because of a persistent urinary tract infection. Her condition satisfied the four criteria for nephrosis and no improvement was achieved by the use of thyroid extract, blood transfusion, urea or decapsulation of the kidneys. The kidneys at operation were pale and soft with no scarring. No biopsy was done. A year later on re-admission she had no oedema but the blood pressure was raised to 140 mm. Hg, the blood urea was 340 mg. % and there was an albumin-

uria of 650 mg. %. She died at home at the age of 2½ years. No autopsy was performed.

Another infant admitted to The Hospital for Sick Children in February, 1958, born after a normal pregnancy and delivery and weighing 5½ lb., developed generalized oedema on the third day of life. (He was the first child of the present marriage of unrelated parents; the mother had had two normal children by a former marriage.) The oedema subsided after two days and recurred at the age of four weeks, leading to admission under the care of a colleague (Dr. A. P. Norman). The infant satisfied the four criteria of nephrosis and electrophoresis showed a typical nephrotic pattern. Urinary amino-acid excretion was within normal range. He was treated with steroids and antibiotics. Very troublesome diarrhoea caused great difficulties in oral feeding and he died after a sudden collapse at the age of 3½ months. Autopsy (Dr. M. Bodian) showed bilateral renal vein thrombosis of long standing with some extension into the inferior vena cava. The changes in the kidneys were those associated with nephrosis.

These five cases illustrate various ways in which nephrosis may be caused very early in life. Poisoning by mercury is another possible factor. The position briefly is that congenital nephrosis or neonatal nephrosis is likely to be due to mechanisms other than those causing the more usual type of nephrosis such as is dealt with in the present report.

Summary and Conclusions

A study of nephrosis as seen at The Hospital for Sick Children during the last 40 years has been made. The cases have been divided into three groups: (1) pre-antibiotic 1917-38; (2) antibiotic, and (3) steroid. The recovery rate in the first group was approximately 50% and much of the mortality was due to infection. In those survivors followed-up in this group there was no instance of relapse after the final hospitalization period. The recovery rate in the second group was 53% and in the third 40%, and in these last two groups the mortality from uraemia was very much higher.

While the control of infection and of water balance has clearly improved the short-term prognosis, none of the other methods of treatment, including short-term steroid therapy, appears to have had any very striking effect on the mortality.

Before there was any method of treatment which strikingly affected the basic sign of proteinuria and its associated biochemical disturbances, attention was focused on the control of infection and on the treatment of oedema. Experience has shown that the treatment of oedema *per se* is not particularly

important except when the oedema is so severe as to be disabling in itself.

The observation that steroids could bring about a complete biochemical remission in the large proportion of cases has switched attention from protective and palliative treatment to the idea of curative treatment. With the advent of steroid therapy therefore the aim has become the complete reversal of all the pathological changes.

The results of various types of therapy have been compared. Until the technique of prolonged (six-12 months) steroid therapy was introduced, no specific therapy appears to have shown any advantage over simple basic dietary therapy and the control of infection with antibiotics.

Results in a small number of cases in whom long continued cortisone therapy has been given suggest, however, that permanent remissions may be obtained by this means, and raise the hope that the suppression of the biochemical disease in this way may reduce the incidence of that secondary nitrogen retention and hypertension which have become the major cause of mortality in recent years.

There is a high natural tendency to recovery. If all avoidable intercurrent incidents are excluded the natural remission rate is between 60 and 70%. In a reasonable proportion of cases of nephrosis spontaneous remission occurs within the first few months of the disease. As there is no evidence in this series that early treatment gives a better prognosis than that obtained when steroid treatment is delayed for some months from the onset of the disease, and since there are undoubted hazards from the use of steroids, it is suggested that steroid treatment of a new case should be delayed for a month or so to exclude the possibility of an early natural remission.

In our view the present aims of treatment should be as follows:

- (1) The control of infection with antibiotics

- (2) The maintenance of nutrition as far as possible with a moderately high protein intake
- (3) The partial control of oedema with a low-sodium (but not a sodium-free) diet
- (4) Long-term treatment with steroids in variable dosage sufficient to maintain urinary protein excretion at the lowest possible level.

By these methods it should be possible to maintain affected children in as good health as possible during the active phase of the disease, and to keep them out of hospital for most of the time, thus interfering with their lives as little as possible.

The success of long-term steroid therapy must be judged by the extent to which it reduces the incidence of renal failure, which has become the major cause of mortality.

Five fatal cases of congenital nephrosis are reported, with varying underlying pathologies.

Thanks are cordially expressed to colleagues on the staff of The Hospital for Sick Children, Great Ormond Street, for permission to include the records of their patients and in some instances to follow up the course of the disease; also to the Department of Medical Illustration for the histograms, and to secretarial staff for much patient typing and re-typing of drafts. The investigations recorded were undertaken under the auspices of the Research Committee of The Hospital for Sick Children.

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POISONING ACCIDENTS IN CHILDHOOD

BY

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The problem of accidents in the home has recently received much publicity and the Government has called for special efforts in dealing with it. Attention is being directed mainly to traumatic causes such as falls, burns and scalds. Of the 900 deaths annually due to domestic accidents in children aged less than 15 years in England and Wales, the vast majority are due to these causes. During the past decade, however, between 16 and 47 (average 32) every year have been due to accidental poisoning and relatively little interest has been shown in this group. Until more is known of the epidemiology of these accidents the problem of prevention cannot be faced.

Paucity of information on the subject is probably due to several factors. The very wide selection of potentially poisonous substances taken by children makes generalization of their effects and sources very difficult. Many poisoning accidents produce no clinical effects (other than parental anxiety) and as a result are not investigated. The fatality rate is very low and does not reveal the extent of the problem.

It is difficult to estimate how many poisoning accidents there are in this country each year. Although there are many papers dealing with small or selected series (Holzel and James, 1951; Spencer, 1951; Craig, 1953) or describing single cases (Kirby, 1955; Hurdle and Lane, 1956; Greenberg, 1957) there is only one large series (Craig and Fraser, 1953) which refers to poisons in general. The fatality rate in this was two in 502 cases. The series described below includes one death in 275 cases. These two series combined show a fatality rate of 0.4% but times, places and possibly case selection differ. Several large series in the U.S.A. (Jacobziner, 1956; Mellins, Christian and Bundesen, 1956; Dobson, Daeschner, Mondshine, Teng, Preble and Knudsen, 1957; Jacobziner and Raybin, 1957; Schroeder, 1957) totalled 14 deaths in about 3,100 children, a fatality rate of 0.45%.

It seems likely, therefore, that for every death, about 250 children are admitted to hospital for observation or treatment of poisoning. This

suggests a total of 7,000 or more such accidents in this country each year. Poisoning thus plays a considerable part in childhood morbidity. Some of the factors in its aetiology are considered below.

Material

The case histories were examined of all children aged less than 16 years who were brought to Hillingdon Hospital because of poisoning or suspected poisoning between January, 1946 and March, 1958. The total number was 292. Seventeen were discarded as being irrelevant to this study of accidental poisoning by ingestion because they referred to coal gas poisoning (8), poisons deliberately taken or given (8) and poison absorbed from a raw skin surface (1). Of the remaining 275 children, 218 were admitted to the wards; the other 57 were treated in the casualty department. No child figured in more than one accident.

There were 156 boys and 119 girls. The average age of the boys was 2 years 10.8 months, that of the girls 2 years 8.2 months, and of the whole series 2 years 9.5 months. The age distribution is shown in Table 1. There was no appreciable difference in

TABLE I
DISTRIBUTION OF POISONING CASES BY SEX AND AGE, JANUARY, 1946-MARCH, 1958

Age (yr.)	Male	Female	Total
	(no.)	(no.)	(no.)
0-1	5	4	9
1-1½	15	10	25
1½-2	37	31	68
2-2½	32	26	58
2½-3	19	14	33
3-4	21	14	35
4-5	11	10	21
5-10	13	10	23
10-16	3	0	3
Total	156	119	275

the age distribution between the sexes. The most susceptible age was between 1½ and 2½ years, this group including 46% of the total.

Incidence

The distribution of the children throughout the period is shown in Table 2.

TABLE 2
NUMBER OF CHILDREN ACCIDENTALLY POISONED,
1946-1957

Year	Number	Year	Number
1946	8	1952	21
1947	7	1953	28
1948	16	1954	25
1949	16	1955	46
1950	16	1956	39
1951	13	1957	32
		Jan.-Mar. 1958	8

The population which the hospital serves has increased only slightly during the period under review. Except at the periphery of the area there has been no alternative hospital for such cases. The annual numbers are therefore approximately comparable and show the great increase in accidental poisoning as noted in Edinburgh and Aberdeen by Craig and Fraser (1953) during the past decade. The peak incidence during this period was in 1955 (see Fig. 1). It is too early yet to determine what the trend over the next few years will be.

Seasonal variation in the incidence of accidental poisoning has been noted in the U.S.A. (Jacobziner, 1956) where 60% of cases occurred in the first half of the year. In the present series a marked variation occurred fairly consistently throughout the period. The pattern however was different. Only 40% occurred in the first six months of the year. More striking was the fact that 57% occurred during the five summer months of May to September (Table 3). This excess in the summer months was not due wholly to the ingestion of seeds, berries and plants, for, of 24 cases of this type of poisoning, 16 occurred in the summer and eight in the winter. It seemed partly related to the longer daylight hours (see below) though the greater wandering about the house which summer warmth permits may have been contributory.

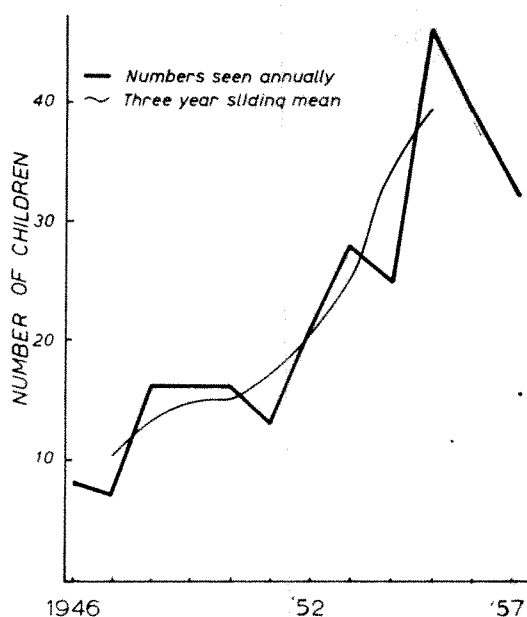


FIG. 1.—Annual numbers of children seen at Hillingdon Hospital because of accidental poisoning, 1946-57

Poisoning accidents occurred at nearly all hours of the day and night. Table 4 shows that the great majority (70%) occurred between 11 a.m. and 7 p.m. Separation of the accidents into summer and winter incidences indicated that there was an excess of accidents between 5 and 7 p.m. during the summer months (Fig. 2). It may be that this summer evening excess can be ascribed to the fact that small children are active for much longer hours in the summer and are likely therefore to be tired and less easily controlled in the evening.

Substances Swallowed

The substances swallowed by the children are listed in Table 5. The total of 285 is accounted for by the fact that one child took three substances and eight took two each.

TABLE 3
NUMBER OF POISONING CASES BY MONTH IN THREE-YEAR PERIODS, 1946-1957

Period	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1946-48	2	1	3	2	1	5	2	7	4	0	1	1
1949-51	2	3	2	2	3	5	2	7	5	9	2	5
1952-54	1	4	3	4	13	9	8	9	9	7	3	4
1955-57	6	3	16	4	8	10	16	14	15	8	7	10
Total	11	11	24	12	25	29	28	37	33	24	13	20

Total for May-Sept. = 152
Total for Oct.-Apr. = 115

TABLE 4
NUMBER OF POISONING ACCIDENTS BY HOUR OF DAY, SUMMER AND WINTER, AND HOURLY INCIDENCE, SUMMER AND WINTER (1946-1957)

Time	Number			Corrected Rate*		Time	Number			Corrected Rate*	
	Total	Summer	Winter	Summer	Winter		Total	Summer	Winter	Summer	Winter
midnight						noon	18	6	12	7.2	10.3
1-						1-	16	5	11	6.0	9.5
2-						2-	12	8	4	9.5	3.4
3-	2	1	1	1.2	0.9	3-	33	18	15	21.4	12.9
4-						4-	25	14	11	16.7	9.5
5-						5-	17	14	3	16.7	2.6
6-	1		1		0.9	6-	22	14	8	16.7	6.9
7-	6	4	2	4.8	1.7	7-	13	7	6	8.4	5.2
8-	13	7	6	8.3	5.2	8-	7	3	4	3.6	3.4
9-	8	6	2	7.2	1.7	9-	5	3	2	3.6	1.7
10-	12	4	8	4.8	6.9	10-	2	1	1	1.2	0.9
11-noon	21	11	10	13.1	8.6	11-midnight					

* Summer (May-Sept., 152 days) and winter (Oct.-Apr., 243 days) numbers have been corrected to represent an hourly incidence per half total period under review

The list is essentially similar to that of Craig and Fraser (1953), though the proportions of the groups of poisons differ slightly. Table 6 and Fig. 3 show the change in the incidence of the various groups throughout the period. Here several differences become apparent.

Within the medicament group several trends are apparent. The frequency of aspirin poisoning has been much enhanced since 1952 by baby type aspirin. Since that year 19 children have been admitted after taking an average of 30 grains of this type of aspirin. Hyoscine, in the form of anti-

motion sickness tablets, has, since about the same time, joined the commonest substances taken. In this area ferrous sulphate is much less often a source of poisoning than in the North. Poisoning with the anti-histamines is also rare. Table 7 illustrates these points. The suggestion that coloured tablets may be more attractive than white ones gains some support from this series. Of the 114 tablets listed, 65 were coloured, 45 were grey or white and in four the colour was not known. In the absence of information on the relative numbers of each available, however, no firm conclusion can be drawn as to why this was so. The only fatality in this series occurred in the following circumstances.

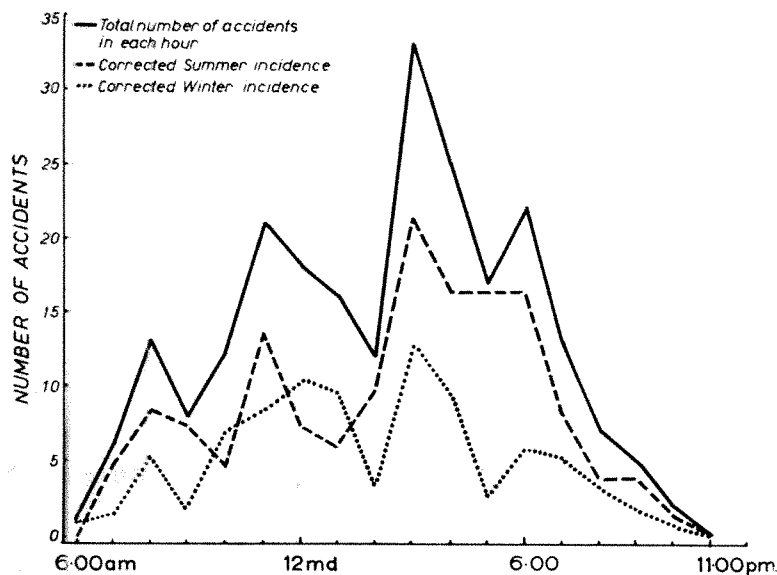


FIG. 2.—Distribution of poisoning accidents throughout day

The great disparity between the increases of accidental poisoning by medicaments and by household materials, clearly shown in the Scottish series, is not seen in this series. In fact, with the exception of 1955, each year has seen an approximately similar rise in both groups.

P.B., a boy aged 22 months, was admitted at about 11 a.m. He had been found one and three-quarter hours previously sucking some white tablets, at that time unidentified, which were kept in an unlocked medicine chest. On admission he was deeply cyanotic, unconscious and convulsing. Death occurred 40 minutes later.

The tablets were later found to contain iron and strychnine.

TABLE 5
ANALYSIS OF SUBSTANCES TAKEN

Substance	Number
(A) Medicaments for internal use	(126)
Aspirin of various types	36
Barbiturates	16
Laxatives	14
Ferrous sulphate, hyoscine	9
Anti-histamines, amphetamine, codeine, vitamin B preparations	4
Anti-convulsants, ephedrine, hypotensives, iron and strychnine, sulphonamides	2
Aconite tablets, digitalis, Dover's tablets, ephedrine and opium mixture, Eumydrin, linctus scillae, phenol mixture, Phosphorine, morphia and atropine tablets, stilboestrol, trinitrin	1
Unidentified tablets	2
(B) Medicaments intended for external use only	(37)
Camphorated oil	6
Surgical spirit, liniments	4
Iodine, eye or ear drops, potassium permanganate crystals, antiseptics	3
Salicylic acid solution	2
Calamine, eucalyptus oil, flavine, formalin, Selsun, Stovarsol, T.C.P., tincture of arnica, contraceptive jelly	1
(C) Household materials	(96)
Disinfectants	17
Cleaning agents	5
Bleaching agents	14
Polishes	7
Turpentine	13
Paraffin	8
Petrol, paint	3
Hair shampoo, nicotine solution, soldering fluid, crayons	2
Brasso, camphor ball, cigarette, creosote, bath crystals, D.D.T. solution, dye, ink, ink powder, match heads, hydrochloric acid, paint remover, photographic developer, phosphorus rat poison, soda, solid fuel, artificial snow pellet, fir-tree oil of each	1
(D) Vegetable substances	(24)
Deadly nightshade berries	15
Woody nightshade berries	2
Laburnum seeds or pods	3
Other seeds or berries	4
(E) Unidentified or unrecorded	(2)
Total	(285)

Source of Poisons

Detailed information was sought from the parents of the last 150 children seen (i.e. all those seen after January, 1954) as to how and where the poisons were obtained. In about half these cases the enquiry was retrospective. Nine could not be traced and eight did not reply. There were five accidents each involving two children; these have been counted as single incidents.

TABLE 6
ANNUAL INCIDENCE BY POISON GROUP

Substance	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	1957
Tablets	3	3	6	5	4	6	7	9	13	21	14	18
All other medicaments	4	0	1	3	4	2	4	3	3	12	9	1
All medicaments	7	3	7	8	8	8	11	12	16	33	23	19
Household materials	2	2	6	4	4	4	9	12	9	15	16	12
Vegetable substances	0	1	2	4	4	1	1	4	0	3	2	2

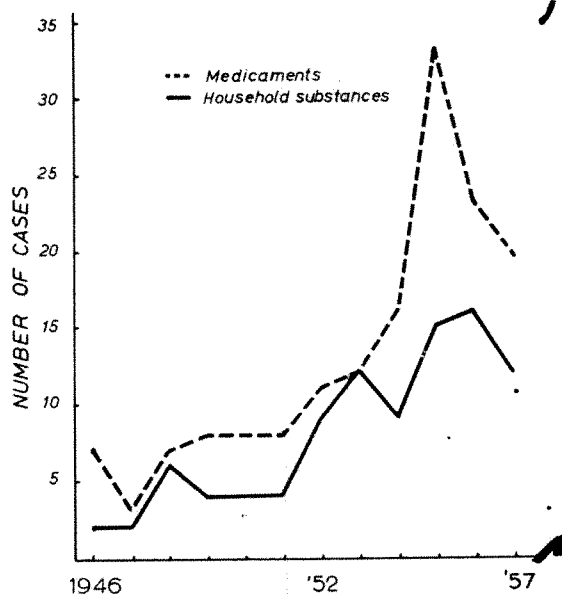


FIG. 3.—Annual incidence of poisoning accidents due to medicaments and household substances, 1946-57

TABLE 7
NUMBER OF ACCIDENTS DUE TO CERTAIN DRUGS, BY THREE-YEAR PERIODS, 1946-1957

Substance	1946-48	1949-51	1952-54	1955-57
Aspirin*	4	1	4	10
Baby type aspirin	0	0	5	14
Barbiturates	1	4	5	6
Laxatives	3	2	3	4
Iron	3	1	3	2
Hyoscine	0	1	4	4

* Including preparations with codeine

Room Concerned. The places in which poisons were obtained are listed in Table 8. In only 12 incidents was the poison obtained from a room other than that where it was normally kept. Comparison with two similar surveys made in the U.S.A. (Jacobziner and Raybin, 1956; Mellins *et al.*, 1956) shows that in this area comparatively fewer dangerous substances were obtained from bedrooms and kitchen, but more from the living rooms.

TABLE 8
LOCATION OF POISONS

Place	Number
Kitchen	38 (26.2%)
Living and dining rooms	35 (24.1%)
Bedrooms	24 (16.5%)
Bathroom	8 (5.5%)
Sheds, garages, greenhouses	8 (5.5%)
Empty rooms, caravans, etc.	8 (5.5%)
Garden	10 (7.0%)
Not known or not recorded	14 (9.6%)

Site within Room. Within rooms there was considerable variation both as to where the poison was kept and where it was actually found (Table 9).

TABLE 9
NUMBER OF POISONS TAKEN BY SITE OF STORAGE AND SITE WHERE FOUND

	Drugs		Household Material	
	Normal-ly Stored	Found	Normal-ly Stored	Found
On tables, dressers, sideboards	6	17	5	21
Open shelves	8	6	16	7
Sills, mantel shelves, draining boards	2	9	1	3
Other open places	0	4	0	10
In cupboards	19	11	19	8
In bathroom or medicine cabinets	13	5	1	1
In drawers	10	9	0	0
No fixed place	4	—	0	—
Not normally kept in household	1	—	8	—
Information not available	19	15	7	4
The same as where stored		35		22
Different place		27		29
Not known		14		6

Excluded from this Table are (a) the vegetable group (7); (b) drugs given in error by parents from column 'Drugs Found' (6); (c) substances the sources of which remain unknown (3).

Clearly, one important factor in the aetiology of accidental poisoning is the frequency with which drugs and household materials are left easily accessible. Though there was a tendency to leave drugs in open positions temporarily rather than permanently, some strange places of storage came to light. A tin box on top of the television set, a dressing-gown pocket and a low, unlocked, glass-fronted cabinet were all used as medicine stores. In 11 of the 35 instances when a medicament was found in its normal place, there were other, sometimes more dangerous, substances present.

It is frequently stated that medicines kept under lock and key are safe from children. Of the 82 incidents involving medicaments, however, this good habit had been invalidated in 14 by various factors. Thus, two locked cupboards were opened, not by the children who took the medicaments, but by elder siblings who had found the keys. In one incident a drawer 'always kept locked' was for once left open,

and in four more the medicament was inadvertently 'left out'. Such situations may be ascribed to carelessness but the following are less easy to condemn. On three occasions drugs just bought were put temporarily with other contents of the shopping basket on the kitchen table before being locked up, only to be found within a few minutes by curious toddlers. Finally, four enterprising opportunists, aged from 11 months to 2 years, grabbed tablets within a few seconds of their being taken out for administration to others.

Height alone seemed to be of little protective value. Fourteen children obtained poisons from shelves or cupboards more than 5 ft. from the ground. No less than 40 are recorded as having climbed to reach the poison. Their average age of 2½ years is slightly less than that of the group as a whole, but boys outnumbered girls by three to one. Three of these children were aged less than 18 months. Perhaps the most ingenious climb was that of R.B. in Example 1.

EXAMPLE 1. R.B., aged 1 year 9 months, climbed up the ill-fitting and partly opened drawers of a dresser in a garden shed. Clinging on to the handles, he reached a bottle of soldering fluid on a shelf 6 ft. above ground.

Some of the value of relative inaccessibility is reduced when parents call medicinal tablets 'sweets' as an inducement to toddlers to accept them. The following examples illustrate some of the above factors:

EXAMPLE 2. S.C., aged 3 years, left his bed at 10 p.m., went into the kitchen, climbed with the help of a chair on to the dresser and opened a high wall cupboard. Ignoring seven other medicaments and disinfectants, he took a substantial amount of flavoured and coloured aspirin tablets. The mother had earlier in the day given him two of these 'sweeties' to help his cold. At the time of this incident both parents heard him but each assumed, being in different rooms, that it was the other who was opening the cupboard.

EXAMPLE 3. S.H., aged 1½ years, was given approximately 60 gr. of ferrous sulphate by her brother, aged 3 years, about 11.30 a.m. He brought a chair from the living room into the kitchen so that he could climb on to the dresser, having first found the key to unlock the top cupboard where mother kept her 'green sweets'.

Container. The variety of container from which the substances were taken was fairly restricted and is shown in Tables 10 and 11.

The pattern is similar to that reported by Mellins *et al.* (1956). On only 11 occasions had the substance been transferred from its original container to one less suitable. The proportion (7%) is much

TABLE 10
TYPES OF CONTAINER FROM WHICH POISONS WERE TAKEN

Container	Number
Bottle	83
Plastic or glass tube	4
Tin	16
Cardboard box	25
Cup or open can	4
Envelope	2
No container	6
Not known	12

TABLE 11
TYPES OF CLOSURE OF CONTAINERS LISTED IN TABLE 10

Closure	Number
Screw cap	67
Cork	20
Plastic bung	2
Fit-over tin lid	4
Fit-in tin lid	3
No closure	10

Cardboard boxes, containers not designed to have lids and instances where there was either no container or where its nature was unknown have been excluded.

smaller than those recorded by Mellins *et al.* (1956) and Jacobziner and Raybin (1956), 40% and 30% respectively. Of these 11, eight involved paraffin or turpentine. It seemed significant that, of the nine bottles or jars without a lid, six contained one of these two substances. As paraffin or turpentine figured in a total of 14 incidents, it appeared that unusually casual handling of them was to some extent responsible for these accidents. This observation apart, study of the containers revealed little of importance. All the common types were represented. Frequently they are most unsafe. Dangerous drugs are supplied in envelopes or flimsy boxes; glass bottles are easily broken, especially when small hands reach high up to grip them; corks can be pulled out by toddlers' teeth when their fingers are not strong enough.

As might be expected, labelling was of little direct importance in the majority of poisoning accidents in young children. In the 14 incidents involving children over the age of 5 years, in only two was the substance labelled. In one instance the child was misled by the wrong label. Adequate labelling, however, ought to warn parents to take care in the storage of harmful substances, yet no less than 27 substances clearly labelled as dangerous were left easily accessible.

EXAMPLE 4. J.H., aged 2 years, took a plastic tube full of hyoscine tablets from a dressing table drawer which was never locked. Asked if the tube was labelled, father replied 'Yes, but it's of no consequence at his age'; yet the label stated 'CAUTION. It is dangerous to exceed the stated dosage'.

Labels such as the above were common. Very few stated unequivocally that the substance should be kept out of reach of children. Indeed one popular brand of analgesic bears a label stressing its safety and harmlessness without a warning of any kind; yet five children swallowed potentially harmful amounts.

Other Factors. Several other factors which occasionally operated are summarized below:

(1) Small children tend to be generous to each other. In this series 14 children were the innocent recipients of dangerous substances. The donors, 22 in number (for several incidents involved more than two children), ranged from 3 to 10 years of age and eight of them were over 7 years old. The older children acted thoughtlessly but not always stupidly and never with malicious intent.

(2) Parents may have their attention distracted by another child or visitor and leave dangerous substances within easy reach of youngsters. Several examples of this were seen.

(3) Children visiting strange houses, which are normally without children, may become bored and wander away from adults to explore drawers or cupboards. This occurred four times.

(4) Whilst parents are moving house or decorating rooms medicines are apt to be left conveniently concentrated in one site, usually on the floor. This led to four accidents.

Conclusions

Nearly all these poisoning accidents occurred because the poison was too easily accessible to young children. Such a situation might be the result of several contributing factors; for example, inadequate furnishing and overcrowding in the home or curiosity, mischief and mental retardation in children. Much the most important factors, however, concerned the parents. Lack of appreciation of the exploratory abilities of children, ignorance of the danger of many household substances, carelessness and apathy in the use and storage of medicaments far outweighed truly accidental causes. This is illustrated by the summary of the causes of the 145 accidents investigated in detail (Table 12).

Though it might seem from this list that all the accidents in groups A to D (numbering 121 in all) could and therefore should have been prevented, this would assume a standard of knowledge, foresight and care far above that found in practice. In Examples 2 and 3 it would be difficult to accuse the parents of carelessness or stupidity. Study of the 120 accidents about which sufficient facts were known (excluding the garden group) suggested that

TABLE 12

HUMAN FACTORS CAUSING 145 POISONING ACCIDENTS

(A) Substances not in normal place of storage	
(1) Adult failed to replace it after use	50
(2) Adult using it at time of accident	15
(3) Adult distracted by other event whilst using substance	7
(4) Family moving house; redecorating room	4
(5) Substance just bought and not yet stored	3
Total	79
(B) Normal place of storage of substance inadequate	
(1) Exploratory ability of child not appreciated by parents	25
(2) Insufficient supervision of child in strange house	4
(3) Poisonous nature of substance not known to parents	1
Total	30
(C) Substance left in misleading container by parents	5
(D) Substance given in error by parents	7
(E) More than one of the above reasons	10
(F) Curiosity of child in garden	7
(G) Source of substance not known to parents	12
(H) Information not available	17

38 (32%) occurred without any obvious parental negligence. The other 82 (68%) seemed easily preventable.

Apart from trying to overcome adult apathy, several simple direct measures are possible. Greater use could be made of short but prominent labels such as 'Keep out of the reach of children'. This is already done by many pharmacists but might be more effective if manufacturers incorporated such a warning on all packages containing medicaments other than those which are harmless even in gross overdosage. Even laxatives can be fatal (Craig and Fraser, 1953). It would also be valuable if similar warnings appeared with the common household poisons such as disinfectants, cleaning and bleaching agents, paraffin and turpentine.

Some accidents would be prevented were the common and dangerous tablet poisons (aspirin, barbiturates, ferrous sulphate, hyoscine and the anti-histamines) always supplied in safety containers. These are merely small tins with snap-closing lids which young children are not strong enough to open. Unfortunately their relatively high cost would preclude their more extensive use. Finally, the tendency to store both medicaments and household materials in unsafe places might be reduced by providing safer storage facilities. Most new houses include several built-in cupboards. It would be neither difficult nor expensive to ensure that at least one in the kitchen and one in, say, a bedroom or the bathroom were fitted with a strong spring catch or similar safety device to defeat young hands.

Summary

The annual number of children accidentally poisoned in north-west Middlesex has greatly increased during the last 10 years. A study of 275 case histories over this period has shown that medicaments and household materials have contributed more or less equally to the rise.

The most susceptible age group was from 1½ to 2½ years of age. Relatively more accidents occurred during the summer months, the excess probably being due to longer daylight hours.

The commonest medicaments taken were aspirin, barbiturates, laxatives, ferrous sulphate and hyoscine. Disinfectants, bleaches, cleaning agents, turpentine and paraffin accounted for over half the household materials.

A more detailed study of 145 incidents showed that children obtained poisons from all parts of the house but most often from the kitchen and living room. Most of the substances taken had not been put away after use, were actually in use at the time, or were inadequately stored. Of this group, enough was known about 120 accidents to suggest that two-thirds could have been readily prevented and that these could be traced to the action (or lack of action) of adults. Predominant were carelessness in handling or storing materials and failure to appreciate the ability of children.

Easily applicable methods which might decrease the number of such accidents include more frequent use of warning labels on drug packages and on the commoner household poisons, greater use of safety containers and provision in all new houses of at least two safety cupboards.

I wish to thank Dr. H. V. L. Finlay for his generous advice and criticism and constant encouragement. I am also indebted to Dr. W. A. Steel for permission to publish this investigation and for the facilities which made it possible. Finally my thanks are due to his secretarial and records staff, particularly Miss M. Burley and Miss M. E. Bates, whose patience and help was much appreciated, and to Miss Beckett for producing the graphs.

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MEGALOBlastic ANAEMIA OF INFANCY IN JAMAICA

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Anaemia in infancy responding specifically to haemopoietic factors present in liver is not common. Between the years 1946 and 1953 a considerable number of cases was reported from the United States of America (Zuelzer and Ogden, 1946) and Italy (Amato, 1946; Pecorella, Burgio and Aversa, 1947). The literature up to 1953 is fully reviewed by Zuelzer and Rutzky (1953). Since that time reports have been rather rare (Freire, 1954; Mouriquand, 1954; Elizavéta, 1955; Morice, Gurzmán and Costa, 1955; Nelson and Creery, 1955; Amato and Di Gruttola, 1956; Gatto, 1957).

Much of the evidence suggests that megaloblastic anaemia of infancy is largely nutritional in origin, and it might therefore be expected that the disease would be common in those parts of the world where malnutrition is still rife. Protein malnutrition is widespread in Africa, the Far East, Mexico, South America and the West Indies (Trowell, Davies and Dean, 1954). Some degree of anaemia is usual in this disease, although an analysis of published material suggests that it is not as a rule severe in uncomplicated cases, since the haemoglobin level averages about 9.0 g.% (Table 1). The anaemia is

most commonly normocytic, although it may be microcytic or macrocytic (Altmann and Murray, 1948). It responds slowly to a protein-rich diet, and the response to liver, vitamin B₁₂ and folic acid has been described as 'poor, indefinite and erratic' (Trowell, 1949). The anaemia is commonly ascribed to protein deficiency associated with liver disease (Woodruff, 1955), although Gómez, Santaella, Galván, Cravioto and Frenk (1954) suggest that it can usually be attributed to an increase in plasma volume.

There have been few bone marrow studies in protein malnutrition. Trowell (1949) states that although at one time he thought that erythropoiesis was commonly megaloblastic, later he changed his opinion and now considers that erythropoiesis is usually macronormoblastic. Lambrecht and Holemans (1952) found some degree of erythroid hypoplasia but no megaloblasts in 24 cases. Woodruff (1955) found a macronormoblastic marrow in six cases. Altmann and Murray (1948) reported megaloblasts and giant stab cells in the marrows of a few of their cases, and Adams (1954) in Durban, South Africa, found megaloblasts in two out of 21 cases and giant stab cells and 'intermediate megaloblasts' in another six cases. Van der Sar (1951) reported one case with megaloblastic erythropoiesis which responded to folic acid. Kho Lien-Keng, Poesponegoro and Poey Seng Hin (1957) studied the bone marrow in 50 cases in Djakarta and reported occasional megaloblasts in six cases and giant stab cells, vacuolated granulocytes or hypersegmented neutrophils in another 26 cases. There was usually erythroid hypoplasia and the response to specific treatment was on the whole poor. Walt, Wills and Nightingale (1950) found no megaloblasts in 36 cases in Durban, but six years later they were able to report 42 cases of megaloblastic anaemia of infancy of whom just over half were also suffering from kwashiorkor (Walt, Holman and Hendrickse, 1956). The following year they described another 18 cases (Walt, Holman and Naidoo, 1957). In Sicily a condition has been described

TABLE 1
AVERAGE HAEMOGLOBIN LEVELS IN KWASHIORKOR

Author	Area	Cases (no.)	Mean Hb (g. %)
Altmann and Murray (1948)	Johannesburg	32	10.2
Walt, Wills and Nightingale (1950)	Durban	36	10.1
Van der Sar (1951)	Curaçao	33	9.3
Trowell and Davies (1952)	Uganda	44	8.5
Gómez, Santaella, Galván, Cravioto and Frenk (1954)	Mexico	51	9.3
Netrasiri and Netrasiri (1955)	Thailand	48	8.7
Woodruff (1955)	Nigeria	6	8.2
Poey Seng Hin (1957)	Djakarta	138	8.9

which resembles kwashiorkor very closely (Gerbas and Burgo, 1955). It usually affects children under 2 years of age who suffer from diarrhoea, often of long standing, and skin changes, dryness of the hair, oedema and hepatomegaly. The liver often shows a severe fatty change, the serum proteins are low and anaemia is common and sometimes severe. Bone marrow studies showed megaloblasts in 10 cases and giant myeloid forms in 20 cases. The typical white cell changes of megaloblastic anaemia of infancy are well illustrated in their paper.

The purpose of this communication is to report 50 cases of megaloblastic anaemia of infancy seen between May, 1956, and November, 1958, and to emphasize that the disease is a common one in Jamaica.

Methods

Standard haematological methods were used (Whitby and Britton, 1957). *In vitro* sickling tests were carried out using a 2% solution of sodium metabisulphite (Daland and Castle, 1948).

Bone marrow was aspirated under local anaesthesia, using an Osgood (16 gauge) needle. The site of puncture selected was the upper end of the tibia about 2 in. below the tibial tuberosity. The marrow films were stained by both Leishman's method and the May-Grünwald-Giemsa technique. A portion of the aspirated material was allowed to clot in the syringe, and the specimen so obtained was fixed and sectioned histologically as described by Mertens (1945). The sections were stained with haematoxylin and eosin, and for iron by the prussian blue technique of Perls. All the sections were stained for iron simultaneously to minimize technical errors.

Results

The age distribution follows closely the pattern of kwashiorkor (Fig. 1) and, of the 50 cases, 32 were boys and 18 girls. Fever, vomiting and diarrhoea were the most common complaints and upper respiratory tract infections were frequent. On examination the most striking finding was that all the children were underweight and many severely so. This is represented graphically in Fig. 2 where the children's admission weights are compared with standard curves based on studies of child health and development made by the Department of Maternal and Child Health, Harvard School of Public Health (Nelson, 1950). In only one instance (Case 12) did the admission weight exceed the third percentile, but even in this case the figure was well below the mean (50th percentile) in the Boston series. Other stigmata of malnutrition were also found; some degree of oedema was present in 30 children, dyspigmentation of the skin was seen in 14 cases, and hair changes were found in 35 cases. The liver was readily palpable in 44 cases and grossly enlarged in seven of these. The spleen was palpable in five instances, but three of these cases also had sickle cell anaemia. Two other cases of sickle cell anaemia were seen and these five infants with sickle cell anaemia and associated megaloblastic anaemia are reported elsewhere (MacIver and Went, 1960). Extreme pallor of the palms of the hands, soles of the feet and mucous membranes was usually present. In summary all the infants in this series were suffering from malnutrition, which ranged clinically from

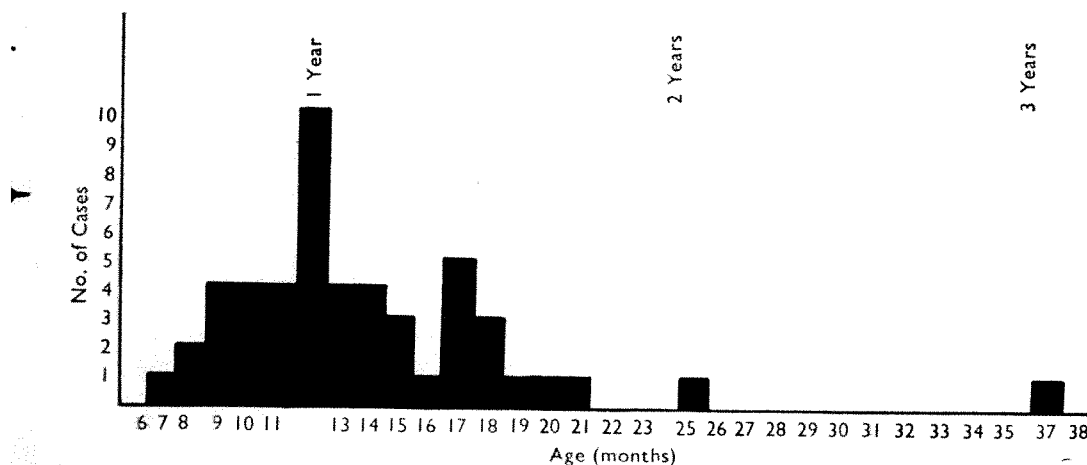


FIG. 1.—Age distribution of 50 cases of megaloblastic anaemia in infancy

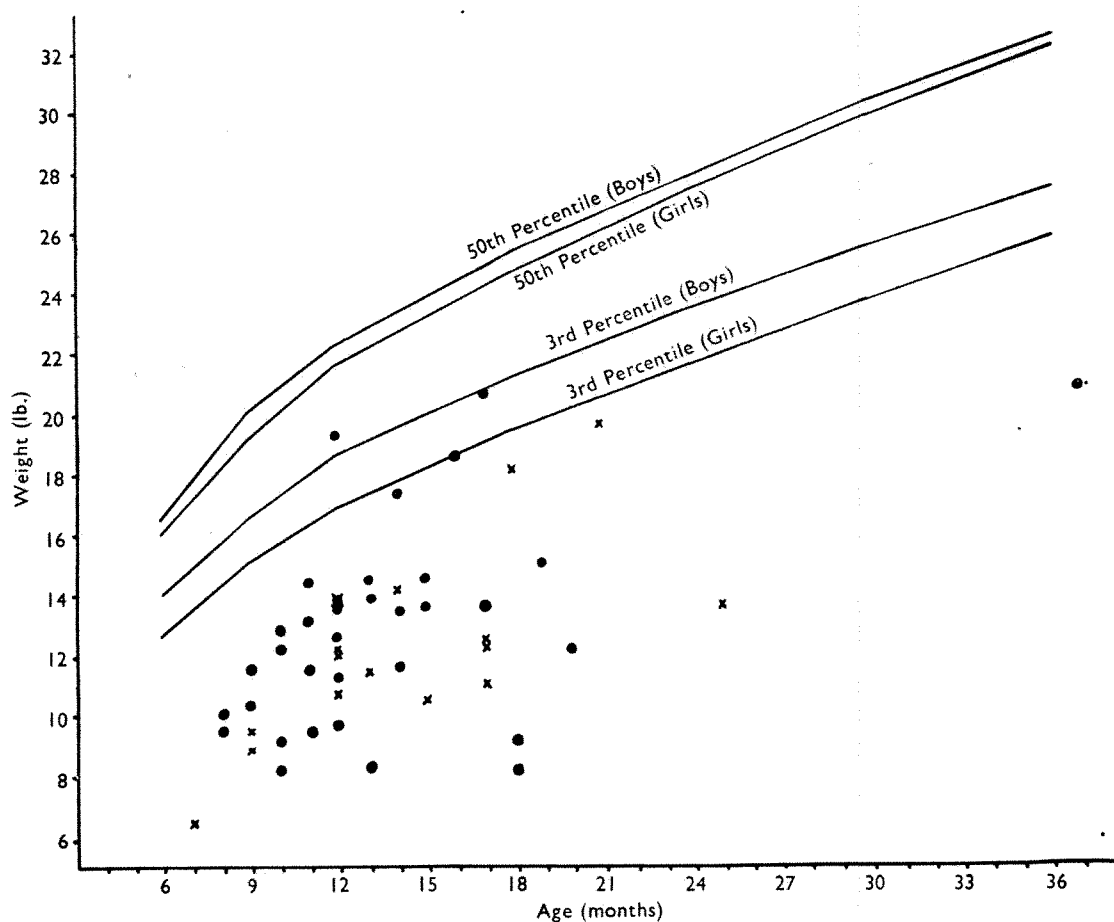


FIG. 2.—Admission weights of 50 cases of megaloblastic anaemia of infancy arranged by age as compared with standard curves for third and fiftieth percentiles prepared by the Department of Maternal and Child Health, Harvard School of Public Health ● boys × girls.

classical kwashiorkor in a few cases to a more marasmic picture in the majority.

The haemoglobin levels on admission ranged from 1.4 to 12.2 g.% but the great majority were very low (average 5.4 g.%). The few cases with high haemoglobin levels on admission developed anaemia in the course of treatment for malnutrition and bone marrow examination was rarely performed until the haemoglobin level had fallen to 7.0 g.% or less. The anaemia was usually normocytic and normochromic in type. Only occasionally was it definitely macrocytic (e.g. Case 48), but sometimes it was hypochromic. The reticulocyte count on admission was normally low, often below 1% (average 2.3%). The serum albumin level was usually low, ranging from 1.2 g.% to 4.4 g.% (average 2.5 g.%). Stool cultures were performed in the great majority of

cases: *S. typhimurium* was isolated in three instances (Cases 8, 9 and 34), *S. St. Paul* was found once (Case 14), pathogenic *Esch. coli* was isolated in five cases (type 0111 in Cases 3 and 29, type 055 in Case 8 and type 026 in Cases 14 and 42) and *Sh. sonnei* was found in one instance (Case 43). Mantoux and V.D.R.L. tests were negative in all cases examined, and the stools were examined routinely for hookworm and other parasites but were negative in every case. Gastric acidity was tested in five cases following the injection of histamine. In two (Cases 45 and 47) some free acid was found, whereas in the other instances (Cases 43, 46 and 50) there was no free acid. Faecal fats were estimated in three cases. In two, normal values were obtained (3g. per 100g. dry faeces in Case 46 and 2.6 g. per 100 g. dry faeces in Case 43). In the other infant (Case 34) a

raised value of 36 g. per 100 g. dry faeces was found, but on follow-up the percentage of fat fell to 14 and then to 6.5 g.% as the child improved clinically. The bone marrow was studied in every case, although in one infant (Case 49) the aspiration was performed 64 hours, and in another (Case 50) 16 hours after the start of oral folic acid therapy. In the majority of instances the marrow was of greatly increased cellularity, although in a few it was hypocellular and fatty. The mean myeloid/erythroid ratio in the whole series was 1.9 to 1, which contrasts strikingly with the findings of Kho Lien-Keng *et al.* (1957) in Indonesia, who found an average myeloid/erythroid ratio of 13.4 to 1.

Bone Marrow Morphology

(1) **Erythropoiesis.** In many instances the picture was indistinguishable from that seen in pernicious anaemia in relapse, and erythropoiesis was frankly megaloblastic (Fig. 3). Not infrequently, however, although megaloblasts were present in sufficient numbers to make the diagnosis beyond dispute, the majority of the erythroblasts were intermediate in type in the sense used by Downey (1952). These are the 'intermediate megaloblasts' of Dacie and White (1949). In such bone marrows erythroblasts could be seen in every stage of abnormality from classical megaloblasts on the one hand, through a variety of intermediate stages to typical normoblasts. In some marrows (e.g., Cases 8, 27, 30 and 31) no classical megaloblasts were seen at all, and although the erythroblasts were still abnormal it was not possible to describe erythropoiesis as other than normoblastic. In such marrows it was still possible to recognize a specific and diagnostic abnormality in the myeloid cells.

(2) **Leucopoiesis.** The granulocyte precursors showed constant qualitative changes which were no less characteristic than those of the erythroblasts. They were usually large and of a bizarre shape. Often they were clearly immature, perhaps premyelocytes or myelocytes, and yet the nucleus had undergone lobulation, indentation and even segmentation. Precise classification was often difficult. Giant metamyelocytes and stab cells were the most easily recognized abnormality and were identical with those seen in pernicious anaemia (Fig. 4). Striking vacuolation of the abnormal myeloid cells was often present (Fig. 5). We agree with Zuelzer and Rutzky (1953) that so far as megaloblastic anaemia of infancy is concerned these white cell changes are pathognomonic. They were seen in every marrow in the series, and sometimes they were unmistakably abnormal even when no typical

megaloblasts could be found. In such cases a therapeutic test with folic acid produced a characteristic reticulocyte response and a sustained haematological improvement. There is no doubt that these changes in the granulocytes provide a sensitive and easily visualized indicator of the early stages of megaloblastic anaemia before the characteristic changes in the erythroblasts have become apparent. We have never seen these white cell changes in iron deficiency anaemia, as reported by Davidson (1952) and Lehmann (1955).

Pathology. Six infants out of the series of 50 died and necropsies were carried out on all of them. In general the findings were those which are typically seen in protein malnutrition in children under 2 years of age in Jamaica (Jelliffe, Bras and Stuart, 1954; Bras, Waterlow and DePass, 1956). An additional finding which was of interest was that extramedullary erythropoiesis was seen in the liver (Fig. 6) in three Cases (3, 28, 43). In two others (Cases 4 and 44) a severe chronic fatty change was present, and in Case 6 an acute fatty change was noted. The immediate cause of death was frequently anaemia and bronchopneumonia.

Liver biopsies were carried out on 12 other infants, and extramedullary erythropoiesis was noted in seven of the 10 biopsy specimens which were sectioned histologically (Cases 13, 15, 16, 21, 22, 23 and 36). A severe chronic fatty change was seen in Cases 16, 23, 29 and 38.

We regard the finding of extramedullary erythropoiesis in the liver as a very characteristic feature of the disease since it has not been observed in several hundred necropsy and liver biopsy specimens from children with malnutrition in Jamaica, unless there was an associated megaloblastic anaemia. It is not, however, always present, and may be difficult to see or completely absent if the liver is very fatty.

Response to Treatment

Of the 50 cases in the series 45 were treated with folic acid and five received vitamin B₁₂. Six of the folic acid-treated cases died. The response to treatment is summarized in Table 2.

Folic Acid Therapy. The response to oral folic acid (5 mg. b.d.) in the 39 patients who recovered was uniformly excellent (Fig. 7). Within one or two days of starting treatment a striking clinical improvement was frequently noted. The increase in appetite and diminution of apathy were very marked and often preceded the reticulocyte response. Vomiting and diarrhoea, which had sometimes persisted for several weeks, were usually brought under control within a few days. A maximum reticulocyte response was

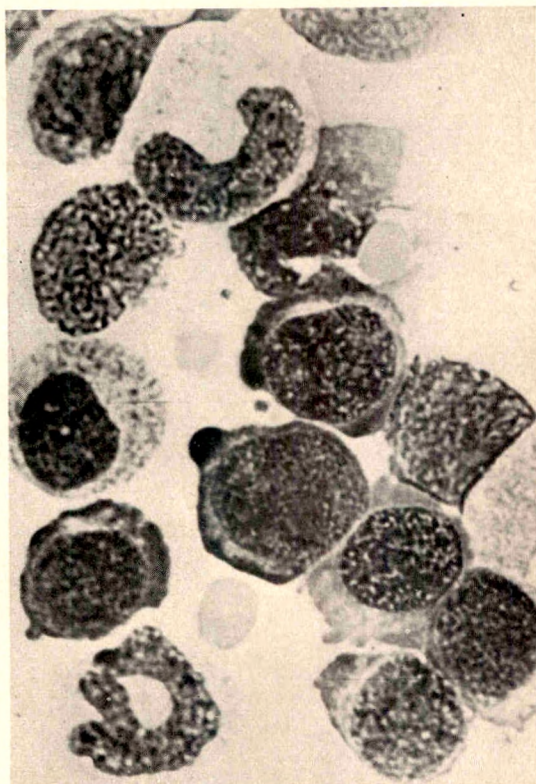


FIG. 3.

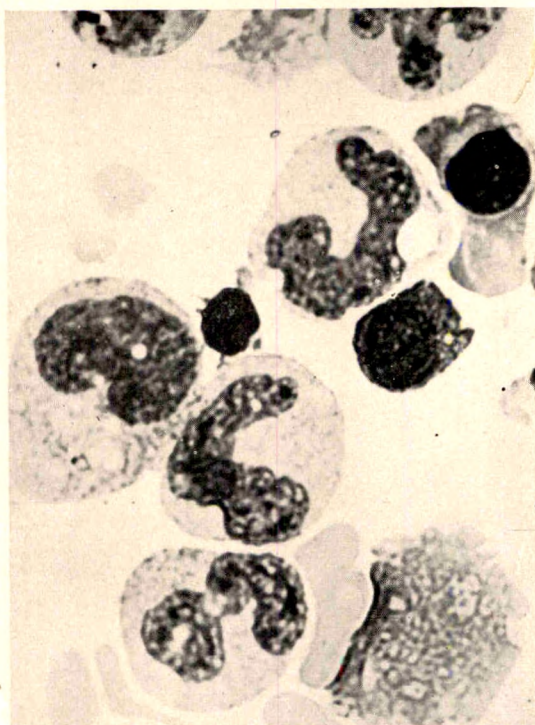


FIG. 4.

- FIG. 3.—Bone marrow from Case 13. ($\times 1200$)
 FIG. 4.—Bone marrow from Case 13 showing giant metamyelocytes and giant stab cells. ($\times 1200$)
 FIG. 5.—Bone marrow from Case 6 showing vacuolated granulocytes. ($\times 1200$)
 FIG. 6.—Necropsy section of liver from Case 3 showing extensive extramedullary erythropoiesis. ($\times 225$)

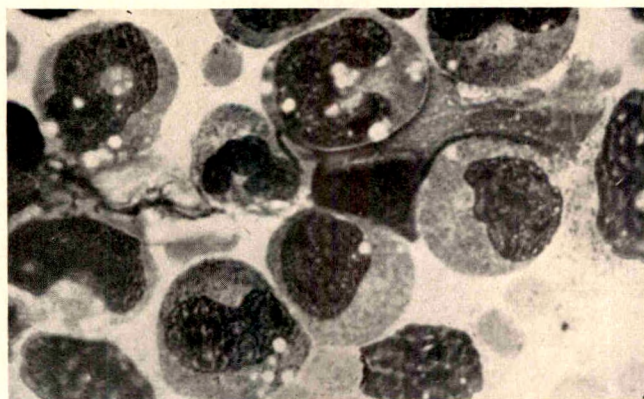


FIG. 5.

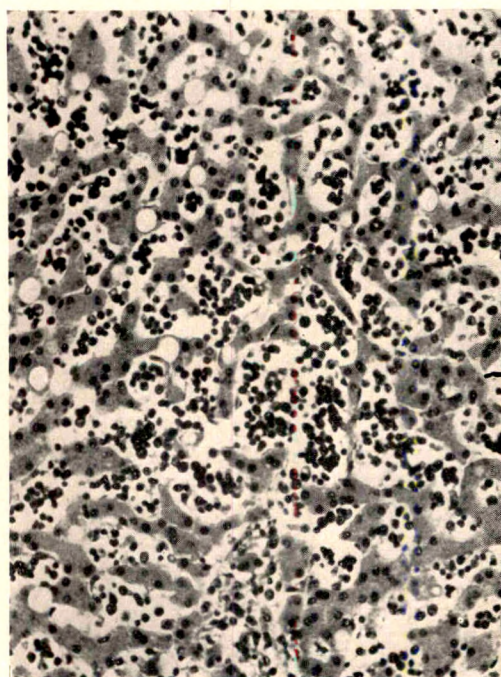


FIG. 6.

TABLE 2
RESPONSE TO TREATMENT (10 MG. FOLIC ACID DAILY, UNLESS OTHERWISE SPECIFIED)

Case No.	Hb (g.%)		Reticulocyte Count at Start of Treatment	Max. Reticulocyte Response (%) and Day after Start of Treatment	Max. Hb Level (g.%) and Day after Start of Treatment	Comments
	On Admission	At Start of Treatment				
1	4.2	4.0	5	17 (5)	10.1 (22)	Transfused (180 ml.) on admission Died suddenly after two days' folic acid therapy Transfused (130 ml.) Died after four days' folic acid therapy
2	2.3	7.5	1	10 (4)	10.1 (9)	
3	3.2	—	2	—	—	
4	3.2	—	0.1	—	—	
5	9.3	6.0	2	20 (9)	8.6 (16)	Died; congenital valve of urethra, pyonephrosis and peritonitis
6	2.8	—	0.2	—	—	
7	9.1	5.4	0.5	8 (7)	12.0 (29)	<i>S. typhimurium</i> and pathogenic <i>Esch. coli</i> (type 055) infections
8	12.2	6.3	0.5	6 (12)	9.5 (12)	
9	12.4	8.6	1	21 (4)	12.7 (11)	<i>S. typhimurium</i> infection
10	5.2	8.3	4	25 (8)	13.3 (24)	Transfused (150 ml.) on admission
11	4.1	6.2	9	32 (7)	8.2 (7)	Also had sickle cell anaemia
12	3.6	3.6	2.5	46 (4)	5.9 (13)	Also had sickle cell anaemia
13	1.4	1.4	0.1	19 (6)	9.4 (12)	Transfused (100 ml.) on admission
14	6.0	6.0	1.0	26 (10)	12.0 (48)	<i>S. St. Paul</i> infection; also pathogenic <i>Esch. coli</i> (type 026)
15	4.9	4.5	0.3	19 (7)	10.5 (31)	Treated with vitamin B ₁₂ , 50 µg. weekly
16	4.7	4.6	—	68 (3)	12.4 (27)	Reticulocyte count 19% two days after start of folic acid therapy
17	4.5	4.5	0.2	28 (8)	12.1 (38)	Treated with single dose of vitamin B ₁₂ (100 µg.)
18	1.8	8.3	1	20 (8)	10.4 (14)	Transfused (250 ml.) on admission; treated with single dose of vitamin B ₁₂ (1,000 µg.)
19	5.6	4.5	2.3	53 (5)	10.9 (18)	Transfused (150 ml.) before first Hb estimation Treated with single dose of vitamin B ₁₂ (1,000 µg.) Also had veno-occlusive disease of liver Transfused (125 ml.) four weeks after admission
20	4.7	4.5	2	26 (6)	10.9 (33)	
21	4.5	3.2	2	24 (7)	9.0 (23)	
22	4.9	6.6	1	49 (5)	9.2 (19)	
23	5.2	7.1	1.2	16 (4)	10.6 (12)	Also had sickle cell anaemia
24	2.7	2.7	0.5	41 (5)	12.2 (39)	
25	6.3	5.0	0.4	50 (15)	8.0 (27)	
26	5.0	5.0	2	37 (5)	9.9 (20)	
27	6.8	5.9	1.5	23 (5)	10.7 (21)	Transfused twice (170 ml.; 150 ml.); died on third day of folic acid therapy Gastro-enteritis due to pathogenic <i>Esch. coli</i> (type 0111), treated with vitamin B ₁₂ (20 µg. on alternate days)
28	3.8	4.8	0.1	—	—	
29	8.0	6.5	5	34 (12)	12.5 (47)	
30	7.0	5.4	4	28 (5)	11.9 (42)	
31	4.3	4.3	11	21 (5)	12.7 (36)	Transfused (220 ml.) on admission <i>S. typhimurium</i> infection; also developed scurvy
32	5.8	5.8	3.8	19 (4)	14.4 (53)	
33	2.8	9.8	0.6	17 (7)	10.4 (7)	
34	11.2	6.2	1	41 (5)	13.0 (65)	
35	6.6	7.1	2	24 (3)	7.2 (5)	Transfused (140 ml.) on admission
36	1.8	6.5	5	28 (5)	11.9 (45)	
37	4.6	4.6	1.6	32 (7)	11.5 (25)	
38	10.7	6.5	1	31 (5)	12.2 (26)	
39	2.3	7.0	1	24 (11)	9.5 (15)	Transfused three times in first week (180, 90, 180 ml.) Reticulocyte count 11% four days after start of folic acid therapy Gastro-enteritis due to pathogenic <i>Esch. coli</i> (type 026) Died after nine days' folic acid therapy Transfused twice (100 ml.; 125 ml.); <i>Sh. sonnei</i> infection Died on third day after one day of folic acid therapy
40	7.3	7.5	1	19 (7)	11.2 (37)	
41	2.7	2.7	—	37 (10)	9.6 (16)	
42	11.2	6.2	1	35 (4)	12.2 (56)	
43	4.4	5.7	2.2	14 (7)	6.2 (7)	Also had sickle cell anaemia Reticulocyte count 30% three days after start of folic acid therapy Also had sickle cell anaemia Transfused (150 ml.) on admission
44	5.0	—	0.1	—	—	
45	7.5	7.0	4	35 (12)	11.8 (31)	
46	3.2	6.9	4.8	59 (6)	9.4 (40)	
47	6.5	6.5	—	46 (5)	9.1 (16)	Also had sickle cell anaemia Transfused (150 ml.) on admission
48	3.2	3.2	12	30 (3)	6.7 (10)	
49	4.5	8.2	0.4	19 (15)	11.4 (42)	
50	3.8	3.8	1	38 (7)	11.2 (32)	

sometimes seen in as short a time as three days and occasionally, particularly in the presence of severe infection, took as long as 15 days (mean six days). The rise in haemoglobin level after therapy was usually quite rapid, and in the 21 cases who received no blood transfusions the rate of increase in haemoglobin ranged from 0.08 g. per day to 0.37 g. per day (mean 0.2 g. per day).

Iron Therapy. Oral iron therapy was usually also required to achieve a sustained improvement, and in

fact some cases were demonstrably iron-deficient from the start as judged by a low mean corpuscular haemoglobin concentration, or more reliably by the absence of stainable iron in the bone marrow. Of the 31 cases in which the marrow was stained for iron, a positive reaction was obtained in 19, although in four of these only a trace of iron was seen. In seven cases ample iron was present (2, 6, 25, 34, 41, 43 and 47) but of these only Cases 6 and 47 had received no treatment before the marrow biopsy; Cases 2, 25 and 43 had been given blood transfusions,

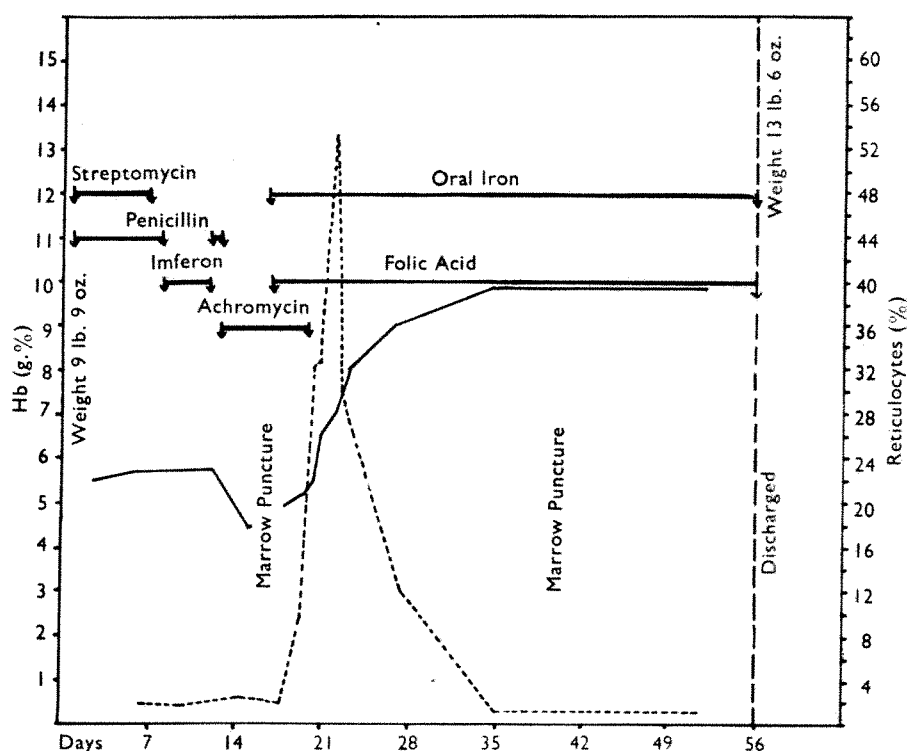


FIG. 7.—Chart of Case 19, aged 9 months, showing typical response to oral folic acid therapy. — Hb - - - reticulocytes

Case 41 had had two days of intramuscular iron and Case 34 had been on oral iron therapy for over three weeks. However, it is noteworthy that in no case was haematological improvement seen on iron therapy alone, and in fact in several instances the infant had been on iron therapy for some time before the marrow was examined, but in spite of that had continued to go downhill. Case 7 received 5 ml. of Imferon but nevertheless the haemoglobin level fell from 9.1 g.% on admission to 5.4 g.% in 38 days. Case 9 was on oral iron whilst the haemoglobin level fell 2.4 g.%, and Case 34 had been on oral iron therapy for 23 days when the marrow was examined, and during this period the haemoglobin level had fallen 2.1 g.%.

Vitamin B₁₂ Therapy. All five cases receiving intramuscular vitamin B₁₂ had a completely satisfactory haematological and clinical response. The dosage varied but was usually on the high side. Case 15 received 50 µg. a week for eight weeks, Case 29 was given 20 µg. on alternate days up to a total of 220 µg. and in the other three cases (17, 18 and 21) a single injection of 1000 µg. was given.

Antibiotics. A high proportion of the infants

were febrile on admission, and many had bronchopneumonia or gastro-enteritis. As a consequence, penicillin and achromycin were not uncommonly given during the first weeks after admission. Since nutritional megaloblastic anaemia in adults sometimes responds to penicillin (Foy, Kondi and Manson-Bahr, 1955), a response in infants might be anticipated. However, in no case was a response observed which could be ascribed to the antibiotic treatment, and in a number of instances the bone marrow aspiration was performed after prolonged use of antibiotics and erythropoiesis was none the less megaloblastic.

Discussion

Megaloblastic anaemia of infancy is a common condition in Jamaica and in 1957 6.3% of all admissions to the paediatric ward of the University College Hospital suffered from the disease. It is clearly a deficiency state, but the origin of the deficiency and what factor or factors are concerned in this deficiency is much less obvious. The ultimate biochemical defect may be of folic acid or its analogues, vitamin B₁₂, or other factors as yet unknown, and the deficiency need not necessarily be the

same in each case. The fact that all reported cases have responded to folic acid, as have all the surviving cases treated with this substance in the present series, does not prove that the deficiency is one of folic acid. The response to vitamin B₁₂ in megaloblastic anaemia of infancy has been more variable; all the children treated with it in the present series responded well, although the dosage in some cases was very high and, according to Frazer (1958), all megaloblastic anaemias will respond to vitamin B₁₂ provided the dosage is high enough. Other workers have reported satisfactory responses (McPherson, Jonsson and Rundles, 1949; Sturgeon and Carpenter, 1950; Zuelzer and Rutzky, 1953) although in some cases the response has been poor (Luhby and Wheeler, 1949; Zuelzer and Rutzky, 1953).

One of the most remarkable things about the history of megaloblastic anaemia of infancy is the almost meteoric rise and fall in the incidence of the condition in the United States. The flood of cases reported in that country between 1946 and 1953 may in part have been due to a 'high index of suspicion', but the virtual disappearance of the disease since 1953 is more difficult to explain. Considerable light was thrown on the aetiology of megaloblastic anaemia in infancy by the work of May and his associates, who undertook a series of experimental investigations on monkeys and showed that a megaloblastic anaemia could readily be induced in these animals by a diet of milk, which has a low content of folic acid, from which ascorbic acid has been excluded (May, Nelson and Salmon, 1949; May, Nelson, Lowe and Salmon, 1950; May, Sundberg and Schaar, 1950; May, Sundberg, Schaar, Lowe and Salmon, 1951; May, Stewart, Hamilton and Salmon, 1952; May, Hamilton and Stewart, 1953; Sundberg, Schaar and May, 1952). In considering the possible causes of folic acid and vitamin B₁₂ deficiency they concluded that 'a chronic deficiency of ascorbic acid leads to a deficiency of folic acid or some difficulty in the metabolism of folic acid or related compounds which results in a megaloblastic pattern in the marrow.' As evidence for this view they cited the high frequency of scurvy (25%) in the case reports of Zuelzer and Ogden (1946) and Aldrich and Nelson (1947).

As a result of the work of May and his associates, the manufacturers introduced large quantities of ascorbic acid (50 mg. per reconstituted quart) into milk formulas which had previously been associated with a rather high incidence of megaloblastic anaemia of infancy (Luhby and Wheeler, 1949), and it is probable that the virtual disappearance of the disease in the United States may, in part at least, be ascribed to this fact. In this connexion it is of interest that

in Zuelzer's last published series of cases (Zuelzer and Rutzky, 1953) milk foods, which had been modified by the sole addition of ascorbic acid, disappeared from the history of infants with megaloblastic anaemia, whereas an unmodified brand persisted.

The importance of ascorbic acid deficiency in the aetiology of the disease in the present series is difficult to evaluate. In only one instance (Case 34) was frank scurvy noted and the deficiency became manifest after the child had been in hospital for 78 days. The infant was malnourished on admission but was not particularly anaemic, even taking into account the dehydration which was present. He had severe gastro-enteritis and *S. typhimurium* was isolated from the stools. Despite courses of achromycin and chloramphenicol the diarrhoea persisted and the *Salmonella* was again found. The child was on a milk diet with the addition of small quantities of orange juice during this period, but the haemoglobin fell steadily from 11.2 g.% to 6.4 g.% after 55 days (Fig. 8). A bone marrow examination at this time showed megaloblastic erythropoiesis, and folic acid was given. A good reticulocytosis and some rise in haemoglobin followed, but soon afterwards the haemoglobin level began to fall again. Clinical evidence of scurvy then appeared and treatment with ascorbic acid (the folic acid was still continued) produced a second reticulocyte response of 20% and a rapid rise in haemoglobin level. In this case there can be no doubt about the importance of ascorbic acid in the proper utilization of folic acid, but, since scurvy is very rarely seen in Jamaica, it is difficult to believe that a deficiency of ascorbic acid can be of aetiological significance in the majority of cases in this series.

There is little doubt of the important part played by infection in the causation of the disease. May *et al.* (1952) were able to produce megaloblastic anaemia in monkeys on a milk diet with adequate amounts of ascorbic acid by inducing turpentine abscesses. It is probable that infection increases the requirements for ascorbic acid. In the present series infections were extremely frequent. A history of recent upper respiratory tract infections or chest colds was elicited in 26 cases, and gastro-intestinal infections were common. Vomiting had occurred in 37 cases, and diarrhoea in 29. As mentioned earlier, specific pathogens were isolated from the stools in several instances, and the importance of gastro-intestinal infections in the aetiology of megaloblastic anaemia is well illustrated by the following case.

Case 9. This 9-month-old infant was admitted with a history of vomiting after feeds for one week and diarrhoea

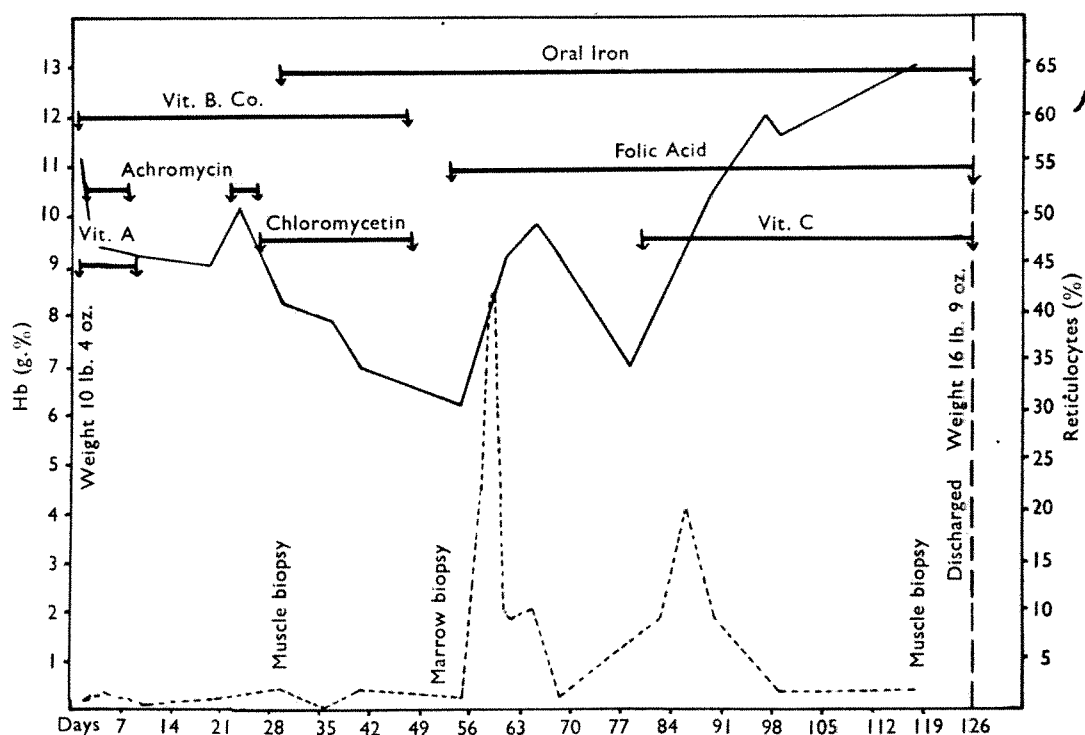


FIG. 8.—Chart of Case 34, aged 8 months, showing fall in haemoglobin level associated with *S. typhimurium* infection, response to folic acid and second response to ascorbic acid (see text). — Hb - - - reticulocytes

for three days. His nutritional state was moderate. *S. typhimurium* was isolated from the stools and despite a course of chloramphenicol the same organism was found again two weeks later. During the course of the first four weeks the haemoglobin level fell from 12.4 g.% to 6.7 g.% (Fig. 9) and, despite treatment with penicillin and streptomycin, he had continual fever. A blood transfusion was given but the haemoglobin level fell again rapidly. On the forty-sixth day the bone marrow was examined and found to be megaloblastic. Treatment with folic acid produced a dramatic result both clinically and haematologically for not only was there a good reticulocyte response and haemoglobin rise, but the fever settled almost immediately and did not recur.

A similar rapid fall in haemoglobin level in infants with gastro-enteritis was observed in Cases 8, 34 and 42.

The mechanism by which gastro-intestinal infections predispose to the development of a megaloblastic anaemia is probably rather complex. In the first place there is the factor of the infection itself, which has already been discussed. Secondly, anorexia and vomiting are frequently associated so that the intake of haemopoietic factors is reduced.

Thirdly, the absorption of these haemopoietic factors may be impaired as a result of persistent diarrhoea. Fourthly, the abnormal bacterial flora in the intestine associated with the infection may lead either to an increased bacterial utilization of these factors or to a reduced synthesis of them.

However important infection and ascorbic acid deficiency may be in the causation of megaloblastic anaemia of infancy, there can be little doubt that the main factor responsible in our series is a dietary deficiency of essential haemopoietic substances. All the infants in the series were underweight, and many were severely so. In addition the features of protein malnutrition were often present. In Table 3 are summarized the diets of the infants in this series, and they are clearly grossly inadequate. Milk, which is the chief staple of an infant's diet during the first year of life, has a low folic acid content, and the heating processes, such as those involved in the canning and powdering of milk, further reduce this small amount of folic acid (Luhby and Wheeler, 1949). Only a few of the infants received any fresh milk and the majority were given only very small

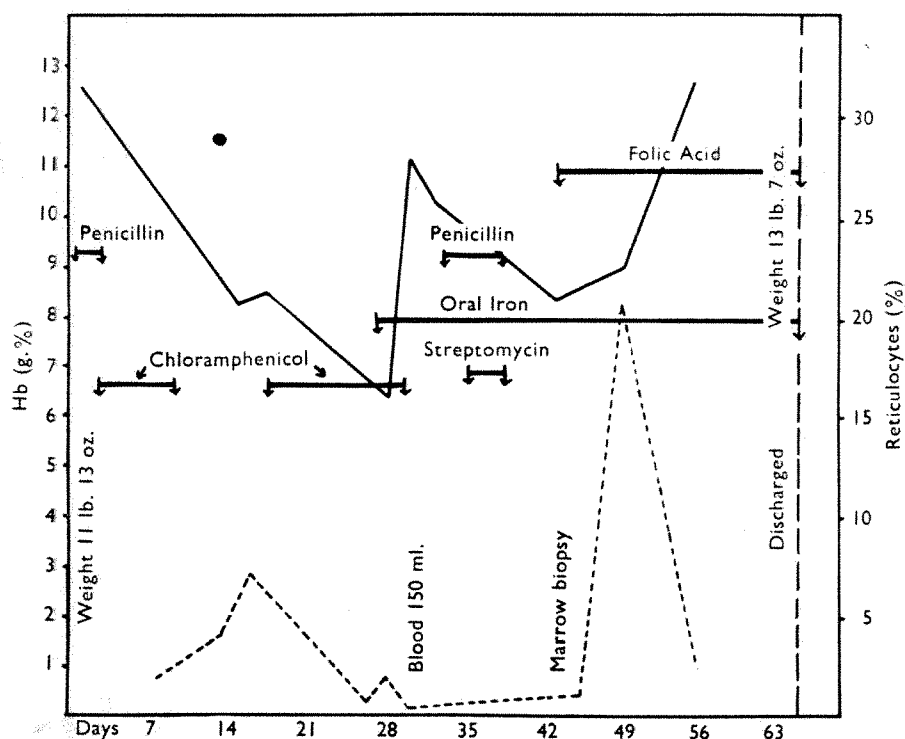


FIG. 9.—Chart of Case 9, aged 9 months, showing fall in haemoglobin level associated with *S. typhimurium* infection and response to folic acid. — Hb - - - - reticulocytes

TABLE 3
SUMMARY OF DIETARY HISTORIES

Case No.	Age (mth.)	Breast Feeding (mth.)	Type of Milk after Weaning	Cereals	Vegetables	Meat	Eggs	Orange Juice	Bush Teas
1	14	7	Skim	Oats	Cho-cho; potatoes	—	Occasional	+	Mint
2	17	6	Skim 2 mth.; Ovaltine	Cornmeal	—	—	—	—	—
3	11	3	Condensed; goat's; skim	Oats	—	—	—	—	Love weed (dodder)
4	13	9	Cow's 2 mth. (none subsequently)	—	—	Beef tea	—	—	—
5	19	9	Lactogen; Cow and Gate	—	—	—	—	+	Love weed (dodder)
6	12	5	Condensed	Oats	—	—	—	—	Mint; Irish-moss (sea-weed)
7	25	9	Cow's	—	Carrot juice	+	+	+	—
8	19	2	Lactogen; Ostermilk; cow's	Cornmeal	—	—	+	+	Mint
9	9	7	Condensed; skim	Oats; arrowroot	—	—	—	+	Mint
10	7	3	Condensed	Barley water	Carrot juice	—	—	+	Irish-moss (sea-weed) linseed
11	12	3	Skim	—	Sweet potatoes; carrot juice	—	—	—	—
12	12	6	Condensed; occ. cow's	Cornmeal	—	Occasional	—	—	Mint
13	17	5	Condensed; occ. cow's	Arrowroot	Occasional	—	Occasional	+	Rosemary; mint
14	20	?	Occ. goat's	—	—	—	—	—	—
15	17	?	?	?	?	?	?	?	?
16	11	4	Skim	Barley water; Quaker oats	—	—	Occasional	+	—
17	12	2	Condensed; occ. powdered	Patent barley; cornmeal; Farex	—	—	—	—	—

(cont.)

TABLE 3—*cont.*

Case No.	Age (mth.)	Breast Feeding (mth.)	Type of Milk after weaning	Cereals	Vegetables	Meat	Eggs	Orange Juice	Bush Teas
18	18	6	Cow's; condensed	Occ. porridge	—	—	—	—	Jack-in-the-bush; susumber
19	9	5	Cow's	Farex	—	—	—	—	Various
20	12	9	Cow's; Ovaltine	Wheat; cornmeal	—	—	—	—	—
21	17	9	Skim; condensed; Cow and Gate	Cornstarch; barley	—	—	—	—	—
22	14	3	Cow's; condensed	Cornmeal	—	—	—	—	Cerosee; love weed (dodder); Jack-in-the-bush
23	13	12	Lactogen	Saltine biscuits	—	—	+	+	Various
24	18	3	Lactogen	Porridge	—	—	—	—	—
25	12	8	Condensed; Ovaltine; skim	Quaker oats	Sweet potatoes	—	Occasional	—	Mint; cerosee
26	17	5	Lactogen; cow's	Cornmeal	—	—	—	—	Mint
27	10	—	Skim; goat's since 5 mth.	Oats	Sweet potatoes	—	—	—	—
28	15	4	Cow's; Milo	Oats	Sweet potatoes	—	+	+	—
29	8	6	Cow and Gate; Ostermilk; condensed	—	—	—	+	+	Irish-moss (sea-weed); linseed
30	9	3	None 1 mth.; cow's 3 mth.; none last 2 mth.	Cornmeal; barley; cornstarch; arrowroot	—	—	—	*+	—
31	14	7	Skim	Oats	—	—	—	+	Mint; Jack-in-the-bush
32	12	9	Condensed	Porridge	Banana	Fish tea	—	—	—
33	21	8	Cow's	Wheat; rice	Yam; sweet potatoes	Fish	+	+	—
34	8	½	None 2 mth.; skim; cow's; condensed	Oats at 3 mth.	—	—	—	Occasional	Mint
35	10	6	Skim	Barley; oats	—	Fish tea	—	—	—
36	15	6	Cow's; Lactogen; skim	Barley; Bemax	—	—	—	—	Mint
37	11	6	Ovaltine; Milo; condensed	Oats; cornmeal; arrowroot	—	—	+	+	Mint
38	9	½	Various proprietary brands; none from 4 mth.	Cornmeal	Green banana	—	—	—	—
39	18	4	Lactogen; Ovaltine	Barley (from oats 1½ yr.	—	—	—	—	Cotton; susumber; mint; Irish-moss (sea-weed)
40	12	6	Lactogen; Horlicks; condensed	Cornmeal	Coconut milk	—	—	—	Milk-weed; negeu; vervine; love-bush; Jack-in-the-bush
41	37	?	Lactogen; all cow's; tried and refused; still bottle fed	Barley water; porridge	Tried and refused	Tried and refused	Tried and refused	Tried and refused	—
42	13	—	Skim; condensed; Vita-cup	—	—	—	—	—	—
43	12	—	Horlicks; Cow and Gate; skim; goat's	—	—	—	—	—	Jack-in-the-bush; White Joseph's coat; God bush; mint
44*	11	?	Condensed; little or none for 3 mth.	Oats; cornmeal	—	—	—	—	—
45	16	10	Cow's; Lactogen	Oats	—	—	—	—	—
46	13	8	Lactogen; condensed; skim	Oats	—	—	—	—	Mint; cerosee
47	12	5	Condensed; skim	Barley water	Spinach; sweet potatoes; cho-cho	—	—	—	Mint
48	14	8	Ostermilk; Milo; condensed	Bread; biscuit	Sweet potatoes	Soup, fish tea	+	—	—
49	12	7	Cow's; Milo	Oats; sago	—	Fish tea	—	—	Mint
50	15	8	Lactogen; Cow and Gate	Barley	Carrot juice	Fish tea	+	—	—

* 3-day dietary survey at home showed intake of 400 calories and 0.75 g. protein per day

quantities of condensed or powdered milk. Goat's milk, which has an even lower folic acid content than human or cow's milk (May *et al.*, 1952), was included in the diet of four infants in this series (Cases 3, 14, 27 and 43). Supplementary foods rich in folic acid, such as meat and green vegetables, were almost totally absent from their diets, which con-

sisted largely of cereals, such as cornmeal, made into a porridge with small quantities of milk, supplemented with a variable quantity of carbohydrate-rich foods such as sweet potato, green banana, cassava and yam. The folic acid content of these foods is not known, but, with the possible exception of green bananas, it is not likely to be high. Vitamin B₁₂

is found in most animal tissues such as meat and eggs, but it is almost completely absent from higher plants. Milk contains a reasonable amount of vitamin B₁₂ but the quantity given to these infants was generally very small, one or two tins of condensed milk being required to last a week or more in most cases. It is therefore quite probable that the children were deficient in both folic acid and vitamin B₁₂, although it seems likely that deficiency of folic acid is the most important factor. In addition to the inadequate intake of haemopoietic substances, the children also received too little protein, and the results of protein malnutrition became manifest. Anorexia was usual and vomiting and diarrhoea were frequent so that the already small intake of haemopoietic substances was further reduced and absorption was impaired.

It is probable that the disease could be quickly eradicated in Jamaica if supplies of milk were more freely available and in particular if the mothers were educated to the importance of including some green vegetables and, if economically possible, meat in the diets of their children in the post-weaning period.

Summary

The literature on megaloblastic anaemia of infancy is briefly reviewed with particular reference to its occurrence in association with protein malnutrition (kwashiorkor).

The clinical, haematological and other laboratory findings in 50 cases of megaloblastic anaemia of infancy are presented. From a clinical point of view the most striking feature is that almost all the infants were very malnourished and grossly underweight. The bone marrow morphology is described, and the diagnostic value of specific changes in the granulocytic series is stressed.

An interesting pathological finding was the presence of extramedullary erythropoiesis in the liver. This was found at necropsy in three out of six cases, and on liver biopsy in seven out of 10 cases. Although not constantly present, extramedullary erythropoiesis is thought to be pathognomonic of the disease.

Of the 50 cases in the series 45 were given folic acid and five received vitamin B₁₂. Six of the folic acid treated cases died. The response to both folic acid and vitamin B₁₂ in the remaining cases was excellent. No response to antibiotics was noted. The pathogenesis of the disease is discussed in some detail and illustrated with cases. Although there is no doubt of the importance of ascorbic acid deficiency and of infection in the aetiology of megaloblastic anaemia of infancy, it seems probable that a dietary deficiency of essential haemopoietic factors is the major cause.

Whether the main deficiency is of folic acid or of vitamin B₁₂ is uncertain at the present time, although in our view a deficiency of folic acid seems likely to be the more important.

The authors are greatly indebted to Dr. J. C. Waterlow, Director of the Medical Research Council's Tropical Metabolism Research Unit, for his permission to include 14 cases which were under his care. They are also very grateful to Professor G. Bras for his advice and assistance with the histology of the liver.

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CONGENITAL THROMBOCYTOPENIC PURPURA

BY

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The purpose of this paper is to present four cases of neonatal thrombocytopenic purpura which have been investigated fully. Although an uncommon condition, it has aroused a good deal of interest and nearly 100 instances have been recorded to date. The literature has been reviewed by Robson and Walker (1951), who collected 52 cases and added three of their own, and also by Morris (1954), who gives references for a further 27 cases and also describes three more under her care. A detailed account of the condition is to be found in Stefanini and Dameshek's text-book *The Hemorrhagic Disorders* (1955).

The original classification of patients with congenital thrombocytopenic purpura into two main groups by Robson and Walker is now generally accepted as a helpful and practical division and is as follows:

Group I.—Infants born of mothers with thrombocytopenic purpura

- (a) idiopathic type (I.T.P.), including mothers who had undergone splenectomy
- (b) secondary or symptomatic type due to drugs, infections, toxæmias, etc.

Group II.—Infants born of normal mothers

Nevertheless this classification may be artificial since there are several instances on record (Sanford, Leslie and Crane, 1936; Urbanski and Hutner, 1942; Finn, 1944) illustrating that a woman may suffer from idiopathic thrombocytopenic purpura (I.T.P.) but be symptom-free and in remission during pregnancy and yet give birth to a thrombocytopenic infant. Unless repeated maternal platelet counts are carried out post-natally, such a case may be incorrectly assigned to Group II. An affected mother may give birth to a normal child (Finn, 1944) or may have dissimilar twins, one affected and one not (Goldstein, 1947). It is also possible that in these congenital cases a genetic fault is sometimes responsible and that fathers as well as mothers could be involved.

A more elaborate classification based on aetiology and illustrating the widely different mechanisms to which congenital thrombocytopenia may be attributable is that of Stefanini and Dameshek (1955). In this, cases are divided into two main groups according to whether megakaryocytes are absent or markedly reduced in the bone marrow (amgakaryocytic), or present in normal or increased numbers (megakaryocytic):

Group I.—Amgakaryocytic

- (1) Congenital hypoplastic anaemia (including the Fanconi syndrome)
- (2) Congenital hypoplastic thrombocytopenia
- (3) Congenital acute leukaemia (usually granulocytic)
- (4) Sepsis, congenital syphilis, other infections, viral diseases, etc.

Group II.—Megakaryocytic

- (a) Children of non-thrombocytopenic mothers
 - (1) Idiopathic thrombocytopenic purpura (rarely present at birth)
 - acute variety
 - chronic variety
 - (2) Erythroblastosis foetalis
 - with demonstrable platelet agglutinins
 - without demonstrable platelet agglutinins
 - (3) Platelet type incompatibility between mother and foetus
- (b) Children of thrombocytopenic mothers
 - (1) Transplacental transfer of platelet agglutinins from mother to foetus (platelet agglutinins as a rule demonstrable in the mother's plasma)
 - (2) Drug thrombocytopenia (transfer through the placenta of both a platelet-destructive factor and the offending drug)

The four cases described in this paper were all the children of apparently healthy non-thrombocytopenic mothers.

Case Reports

Case 1. (Fig. 1.) Paul B., a male child, was delivered at full term. The mother had had rubella at the eighth week of pregnancy and a purpuric rash appeared on the child's trunk, face and limbs within 15 minutes of birth (Figs. 2 and 3). He had various congenital defects, including penile hypospadias, a heart lesion and a cataract. On the first day after birth the platelet count was 56,000/c.mm.; the bone marrow showed very scanty megakaryocytes (Fig. 4) and those present had an atypical lymphoid appearance and seemed indolent as regards platelet production (Figs. 5 and 6); erythropoiesis was active; no platelet agglutinins were demonstrable in the infant's serum nor in the maternal serum put up against the infant's platelets. The platelet count after some fluctuation fell to 36,000/c.mm. on the eighth day. On the following day prednisolone was commenced and there was a satisfactory response in the platelet count which rose to normal and has remained normal since. A second marrow examination carried out about one month after birth, whilst the platelets were increasing, showed numerous megakaryocytes of normal morphology (Fig. 7). This child showed no significant anaemia.

Case 2. (Fig. 8.) Andrea H., a female child, was born at full term. About six hours after delivery a petechial rash was noted, mainly on the face and in the skin creases but also scattered over the trunk and limbs. Her initial platelet count on the second day was 96,000/c.mm. The bone marrow on the third day showed a paucity of megakaryocytes; of those present some were of an intermediate type with granule formation whilst others were of the lymphoid variety, both devoid of platelet formation. Erythropoiesis was active. No platelet agglutinins were demonstrable in either the infant's or the mother's serum. The platelet count had dropped to 40,000/c.mm. by the fifth day when prednisolone was commenced. There followed a rapid rise in the platelet count which has remained normal. No anaemia was present.

Case 3. (Fig. 9.) Stella H., a second-born female child, was delivered at full term. Four days after birth she passed a small amount of blood per vaginam. Nine days after birth there was a large bruise on the left leg and it was noted that there was a tendency to bleed easily from a scratch over one eye. On the following day a small bruise appeared on the right leg. On the tenth

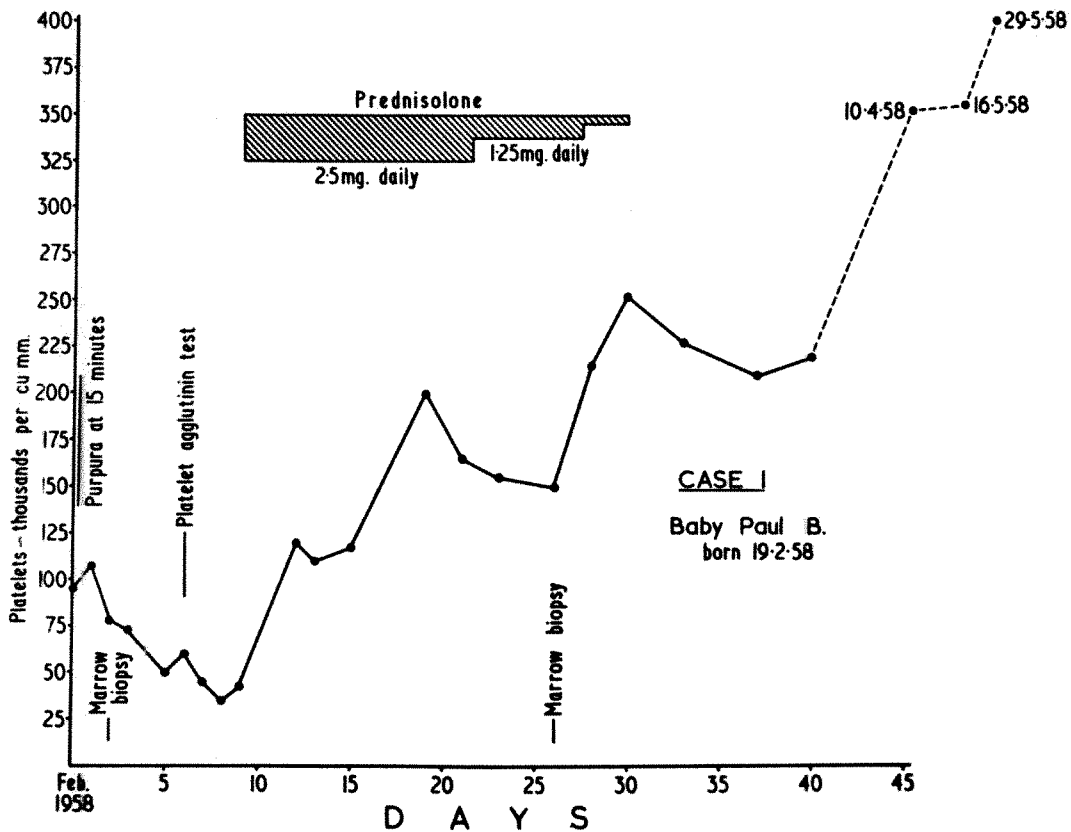


FIG. 1.—Case 1.



FIG. 2.



FIG. 3.

FIGS. 2 and 3.—Case 1.

FIG. 4.—Case 1. Smear of tibia marrow taken one day after birth $\times 175$. (Marrow findings in Cases 2 and 3 during thrombocytopenic phase were similar.)

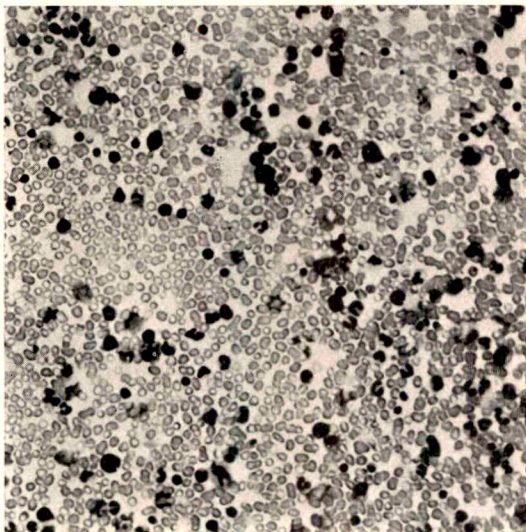


FIG. 4.

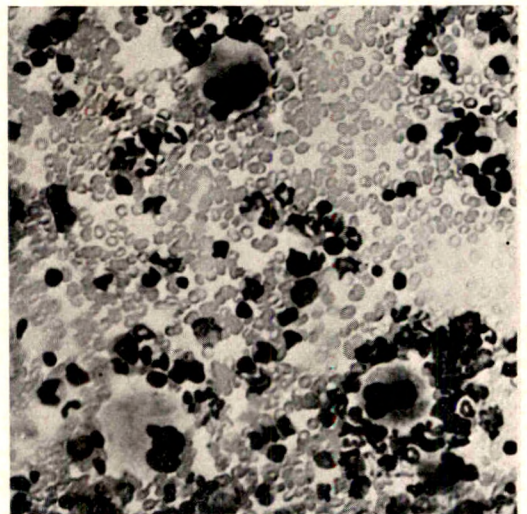


FIG. 7.

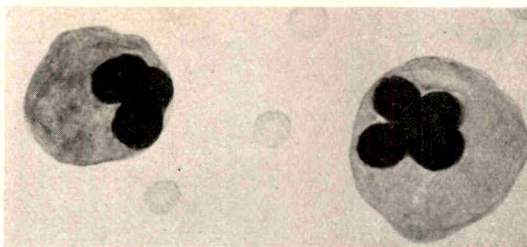


FIG. 5.

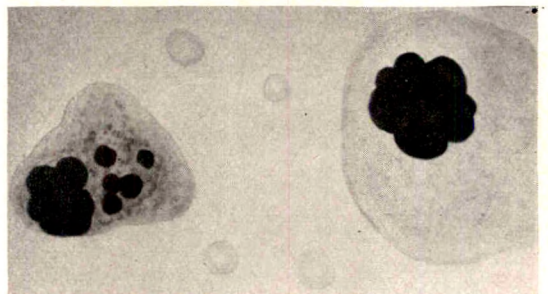


FIG. 6

FIGS. 5 and 6.—Case 1. Drawings of 'intermediate' and 'lymphoid' types of megakaryocytes present in tibia marrow smear. $\times 800$.

FIG. 7.—Case 1. Smear of tibia marrow taken 26 days after birth when platelets had risen to 152,000 per c.mm. $\times 220$.

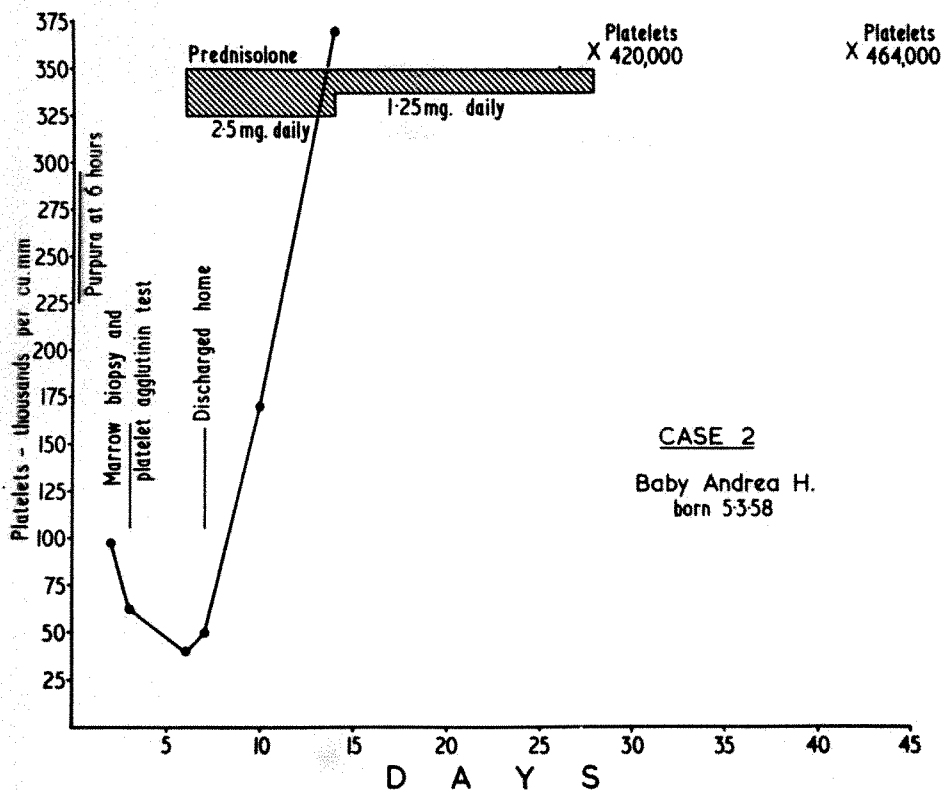


FIG. 8.—Case 2.

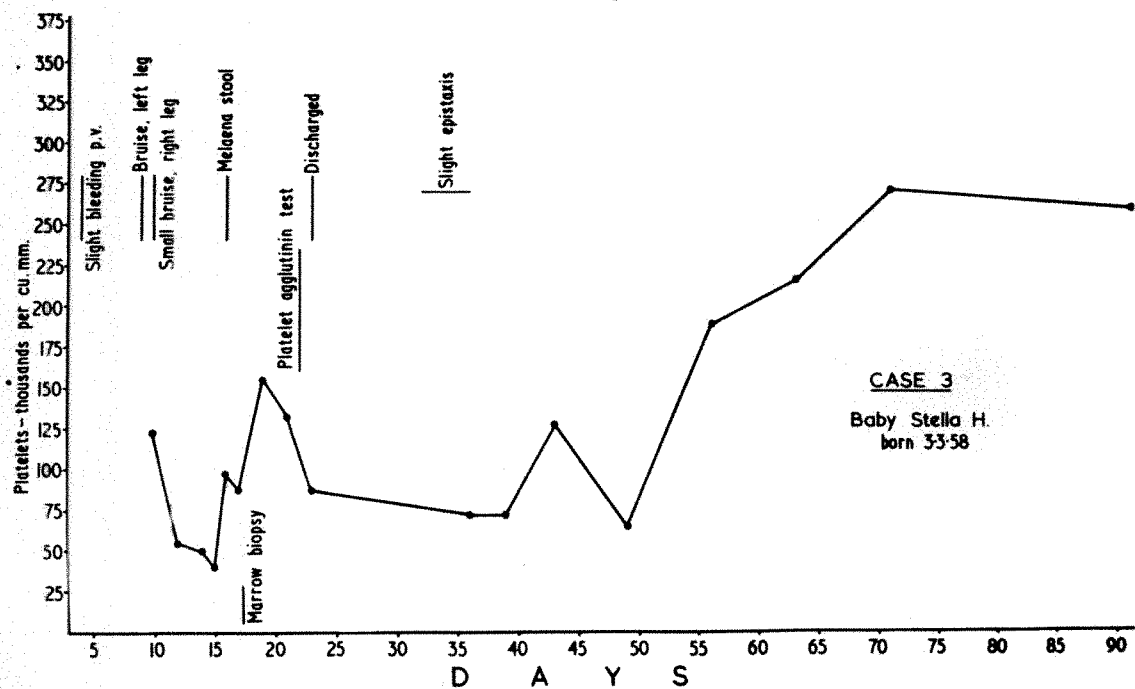


FIG. 9.—Case 3.

day after birth the platelet count was 124,000/c.mm., falling to 39,000/c.mm. during the succeeding five days. On the sixteenth day the child passed a melaena stool which soon cleared. No purpura was seen. A marrow examination carried out on the seventeenth day when the platelet count was 89,000/c.mm. showed scanty megakaryocytes again of intermediate and lymphoid types with little platelet production. Platelet agglutinins against her own platelets and those of a normal compatible control were demonstrable in the infant's serum when tested on the twenty-second day of life but the maternal serum failed to agglutinate the child's platelets. These results were also confirmed in a subsequent test. The child was discharged aged 23 days and after some fluctuations in the platelet count, associated with mild epistaxis when it stood at 72,000/c.mm., there was a gradual return to normal and the child had no haemorrhagic manifestations. She made a spontaneous recovery, no cortisone therapy being given.

Case 4. (Fig. 10.) Stephen H. was a brother of the previous patient and was three and a half years older. They were the only children of the marriage. Eleven days after birth he had an epistaxis of three to four days'

duration and the platelet count was found to be 83,000/c.mm. It subsequently fell to 63,000/c.mm. and then rose quickly and spontaneously to a normal level, since when the boy has remained well. Tests carried out in April, 1958 showed a normal platelet count of 308,000/c.mm., and no platelet agglutinins were demonstrable in his serum against his own platelets or those of a normal compatible control. The mother's serum also failed to agglutinate his platelets. No marrow biopsy was performed in the thrombocytopenic period shortly after birth and it was felt that no useful information would accrue by doing this after three and a half years when the boy was normal.

The familial aspect of these last two cases is very interesting.

Table 1 sets out the significant findings in the four cases described.

Additional Significant Observations

A family history of a bleeding tendency was obtained only in Cases 3 and 4. In the six parents

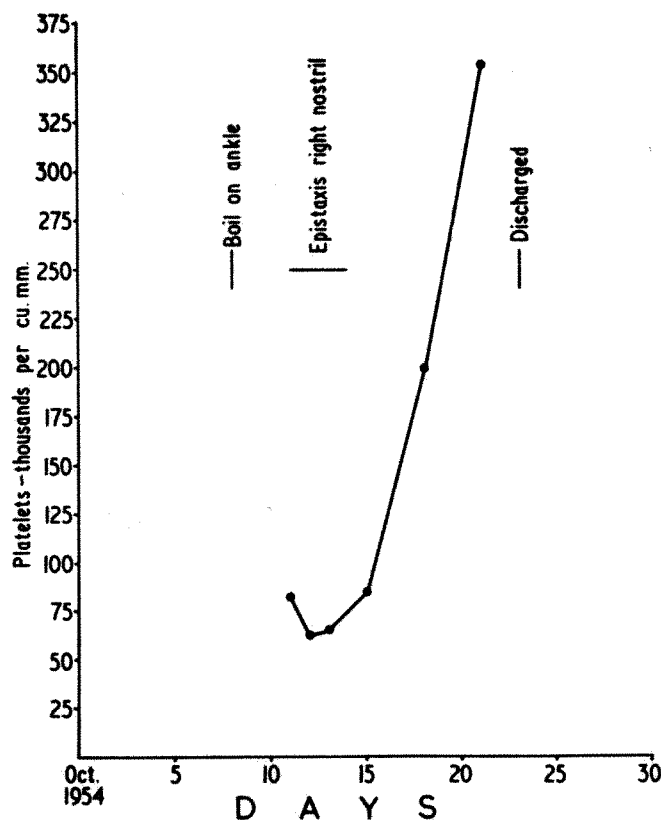


FIG. 10.—Case 4.

CASE 4

Baby Stephen H.
born 1-10-54

TABLE 1
CLINICAL DETAILS

Case	Age when Lesions Appeared	Site of Bleeding	First and Lowest Platelet Count (no./c.mm.)	Day of Lowest Count	Marrow Biopsy and Age	Platelet Agglutininations in Infant and Mother	Mother's First Platelet Count after Delivery (no./c.mm.) and Day
1 Paul B.	15 min.	Skin (purpura)	56,000 36,000	8	Megakaryocytes present but scanty; morphology as in I.T.P. (1 day) Megakaryocytes in normal numbers; morphology normal (26 days)	None	365,000 (1)
2 Andrea H.	6 hr.	Skin (purpura)	96,000 40,000	5	Megakaryocytes present but scanty; morphology as in I.T.P. (2 days)	None	286,000 (2)
3 Stella H. (sister of Case 4)	4, 9, 10, 16, 32 days	Vagina, skin (bruising), intestine, nose	124,000 39,000	15	Megakaryocytes present but scanty; morphology as in I.T.P. (17 days)	Present in infant against own platelets and those of normal control; mother—negative	658,000 (10)
4 Stephen H.	11 days	Nose	83,000 63,000	12	Not examined	Not tested at birth; none aged 3½ years	386,000 (12)

of the three families involved and in their relatives there was no suggestion of any haemorrhagic diathesis and platelet counts carried out on two or more occasions on each of the mothers were all within normal limits. No evidence of erythroblastosis foetalis was present clinically in any of the children shortly after birth. Anaemia was not a feature and the Coombs test in Cases 1, 2 and 3 was negative. All three mothers were Rhesus (D) positive, had negative Wassermann and Kahn reactions and were taking no drugs. Hypoprolthrombinaemia was excluded and in none of the infants was there any prolongation of coagulation time. The spleen was palpable only in Case 1.

The purpura in the first two cases disappeared within a week to 10 days as the platelet count rose following the administration of prednisolone. In Cases 3 and 4 (sister and brother), where haemorrhage involved other sites, recovery was spontaneous and also rapid. The marrow biopsies were obtained by aspiration from the tibia. The platelets were counted by the Lempert technique, and platelet agglutinins were tested against suspensions of platelets in both saline and albumen.

Discussion

The four cases recorded were the offspring of apparently healthy non-thrombocytopenic mothers (Group II in Robson and Walker's original classification). Even allowing for the fact that a

woman with idiopathic thrombocytopenic purpura (I.T.P.) may remit and be symptom-free during pregnancy, there was nothing to suggest this possibility in any of these mothers.

A marked reduction in megakaryocytes was a common feature in all three marrow examinations made during the early thrombocytopenic stage and this was unassociated with any general hypoplasia. This congenital hypoplasia of megakaryocytes accompanied by the morphological features already described suggests that the term 'congenital hypoplastic thrombocytopenia' may reflect the true nature of the condition and be a real entity (Hauser, 1948; Landolt, 1948). It is of some significance that Case 1 did in fact have other congenital lesions and that megakaryocytes appeared in normal numbers coincident with recovery. The familial incidence in Cases 3 and 4 is also compatible with a congenital aetiology, although in the first of these the finding of a platelet auto-antibody suggests some immune mechanism, as is often seen in chronic I.T.P. In the latter condition, megakaryocytes are characteristically plentiful in the marrow, and their paucity must be a strong point against this diagnosis. However, in two reported cases (Whitney and Barritt, 1942; Finn, 1944) of neonatal purpura occurring in infants of mothers with I.T.P., presumed but not proved to be due to an immune mechanism, the infant's marrow was found to be deficient in megakaryocytes at autopsy. There was

no suspicion of I.T.P. in the history of the mother of Case 3; she was also the mother of Case 4 and in each pregnancy her platelet count was normal. In both infants the somewhat late onset of symptoms (the fourth and eleventh day after birth respectively) also suggests that the cause was not related directly to the mother. It must be admitted that the serum of the elder child in this family (Case 4) was not tested for platelet antibodies at or shortly after birth. There was only a negative result at 3½ years of age, long after the thrombocytopenia had subsided, and this must be regarded as inconclusive. It is possible that these two children could be instances *de novo* of familial idiopathic thrombocytopenic purpura, although the marrow finding in the younger child is against this, and it is very unusual for this disease to manifest itself at such an early age.

Most cases of congenital hypoplastic thrombocytopenia recover rapidly and even spontaneously, although the administration of prednisolone in Cases 1 and 2 appeared to result in a rapid rise in the platelet count. Even in Case 3, where the megakaryocytic hypoplasia was associated with the demonstrable presence of a platelet antibody, recovery was rapid and unaided. The degree of megakaryocytic hypoplasia is probably an important factor in recovery since in the virtually complete amegakaryocytic types described by Greenwald and Sherman (1929), Bell, Mold, Oliver and Shaw (1956) and Emery, Gordon, Rendle-Short, Varadi and Warrack (1957), the outcome was fatal, there being no response to cortisone or splenectomy where this was tried, and there were other congenital malformations. In spite of the good prognosis in congenital thrombocytopenic purpura, provided the infant has survived the trauma of birth and provided the condition is not secondary to some infection, there is always the remote risk of the serious complication of intracranial haemorrhage, particularly when the platelet count is at a very low level and showing no tendency to rise. It is this hazard which makes treatment important. The chances of therapeutic success with either cortisone or splenectomy will depend ultimately on the degree of megakaryocytic

hypoplasia and should be tried in this order. If megakaryocytes are completely lacking no beneficial effect can be anticipated and splenectomy is contra-indicated.

Summary

Four babies with congenital thrombocytopenic purpura, whose mothers were apparently normal, have been reported. No agglutination was demonstrable between the sera of these mothers and the platelets of their babies. A platelet agglutinin was found in one infant. The marrow findings in three of the cases pointed to a congenital hypoplasia of the megakaryocytes, and in one instance a return to normal numbers and morphology concurrent with recovery was noted.

We wish to thank Dr. C. F. Harris and Dr. A. W. Franklin of the Paediatric Department of St. Bartholomew's Hospital, London, for permission to record these cases which were under their care, and we are also indebted to Miss B. Kirk for technical assistance in the haematological investigations.

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NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE) OF THE VERTEBRAL COLUMN

BY

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(RECEIVED FOR PUBLICATION JUNE 1, 1959)

Although the occurrence of bone changes in von Recklinghausen's disease is uncommon, the incidence is difficult to determine, as mild cases are less likely to seek advice, particularly if the disease is already in the family. Holt and Wright (1948) thought it was greater than a previously estimated figure of 7%.

Of the bony deformities, scoliosis appears to be the commonest. Weiss (1921) described 15 cases of neurofibromatosis, all of whom had scoliosis. Brooks and Lehman (1924) studied seven cases with bone changes and found that all had scoliosis. They suggested that the lesion began with a neurofibroma of the periosteal nerve, and that this set up a reaction in the vertebra with bone destruction and regeneration. If actively bone-forming periosteum covers the tumour, a thin shell of bone forms over it and gives a cystic appearance. Weber (1930) described further cases and discussed various aspects of neurofibromatosis. Hagelstam (1946) reviewed the literature and collected 37 cases with deformity of the spine: two were in the cervical region, 20 in the upper and mid-dorsal regions and 15 in the dorsolumbar spines. Holt and Wright (1948) reviewed 127 cases of neurofibromatosis of which 29% showed skeletal involvement. The bone lesions consisted of erosive defects, scoliosis, growth disorders, bowing and pseudoarthrosis of the lower leg, intrasosseous cystic lesions and associated anomalies. McCarroll (1950) found 19 cases of scoliosis in 43 cases with bone involvement.

Below are case reports of five children with neurofibromatosis of the spine.

Case Reports

Case 1. This girl was first seen at the age of 16 months on account of a 'bump in the back' which had been noticed from the age of 3 months. She was able to say several words with meaning and had learnt to sit without support at 10 months. She was unable to walk.

The father, who was the youngest of 17 children, and

his father had von Recklinghausen's disease, but as far as we could tell the father's siblings were unaffected. We did not, however, examine them. Our patient was one of two children, both of whom had the disease.

On examination the girl presented the typical appearance of von Recklinghausen's disease with involvement of the vertebrae (Figs. 1 and 2). There were large pigmented and nodular areas in the groins (Fig. 3) and a severe kyphosis of the upper lumbar spine with chest deformity. Radiographs showed upper lumbar scoliosis with increased density and translucent areas in the anterior and posterior surfaces of the vertebrae (Fig. 4). There was considerable widening of the neural canal, suggesting the presence of a tumour mass. There was a spastic paraplegia with exaggerated tendon jerks, bilateral ankle clonus and a bilateral extensor plantar response. The neurosurgeon was not prepared to operate.

The girl subsequently put words together into sentences at 2 years and walked without help at 2 years and 3 months. At the age of 5 years she developed a headache, mainly occipital, and ataxia. She became drowsy and could no longer walk. On examination bilateral papilloedema was found, and a diagnosis of intracranial neurofibroma was made. She died at home.

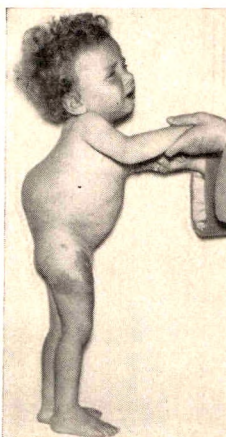


FIG. 1.—Case 1, aged 16 months.

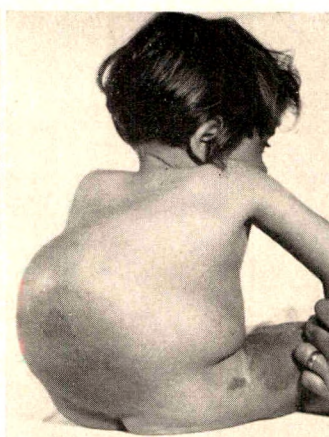


FIG. 2.—Case 1, aged 4 years.



FIG. 3.—Case 1, showing pigmented and nodular areas in groins.



FIG. 5.—Case 2.

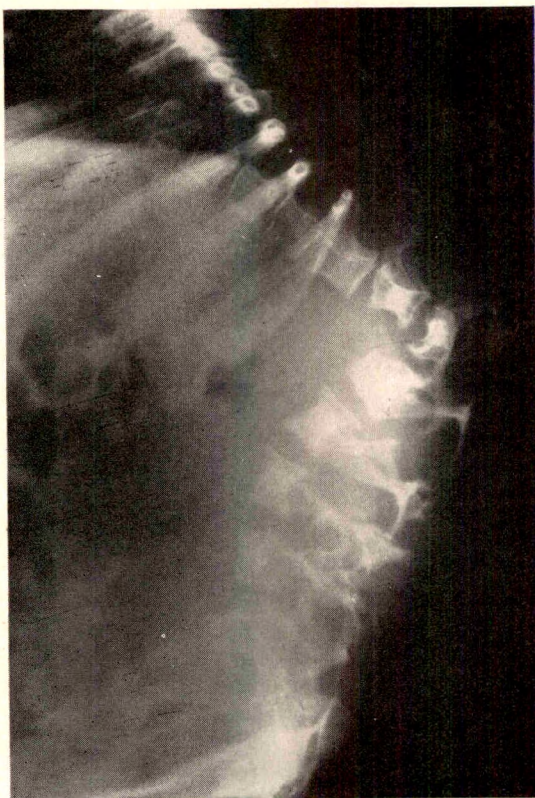


FIG. 4.—Case 1.



FIG. 6.—Case 2, close-up photograph of affected skin.

Case 2. This girl was under the care of an orthopaedic surgeon from the age of 6 months on account of dorsolumbar kyphosis. She was referred to a paediatrician at the age of 12 years because of cyanosis and dyspnoea on exertion. She had been brought up in a children's home from the age of 6 months having been neglected by the parents. The family history was unknown.

On examination at the age of 12 years there was a severe kyphosis maximal in the lower thoracic region (Fig. 5). There was widespread brown discolouration of the skin involving the lower half of the trunk, buttocks and part of the thighs. The skin in these areas was raised and pedunculated (Fig. 6). No other abnormal physical signs were found.

A radiograph of the vertebrae showed exaggerated pedicles (Fig. 7) and that of the left femur showed patchy calcification and cortical destruction (Fig. 8). A chest

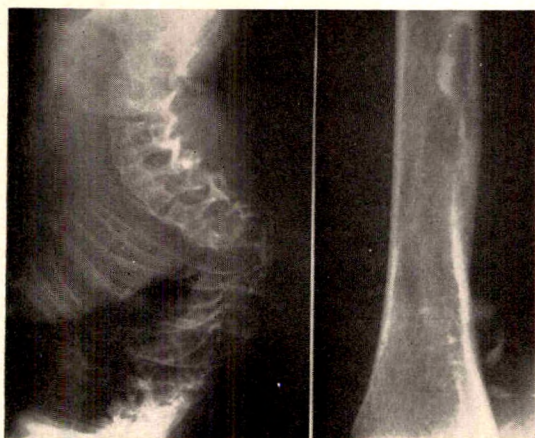


FIG. 7.

FIG. 8.

FIGS. 7 AND 8.—Case 2.

radiograph was normal and it was concluded that the respiratory symptoms were due to thoracic deformity. Skin biopsy confirmed the diagnosis of neurofibromatosis.

Case 3. (Figs. 9-11.) Swellings of the neck were noticed in this boy at 11 months. At the age of 14 months he was seen at the Leeds General Infirmary. There was a bilateral cervical adenitis with mottling of the skin. A radiograph showed collapse of the body of the fourth cervical vertebra. The tuberculin test was negative. Biopsy of the gland mass gave the appearance of a neurofibroma.

He was immobilized on a plaster of paris bed with headpiece from 2 years 2 months to 5 years 10 months, by which time the neck was grossly swollen by a nodular mass which in places infiltrated and reddened the skin. The area was generally freckled and pigmented and on the trunk there were café-au-lait patches. Radio-

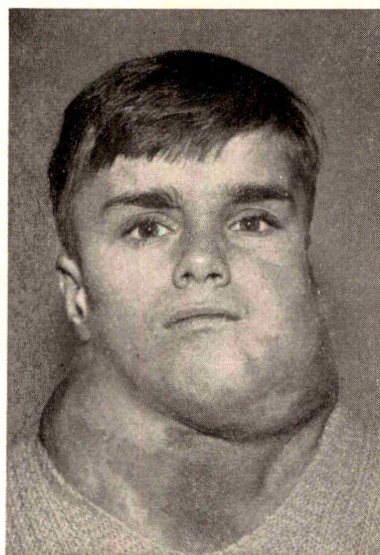


FIG. 9.—Case 3.

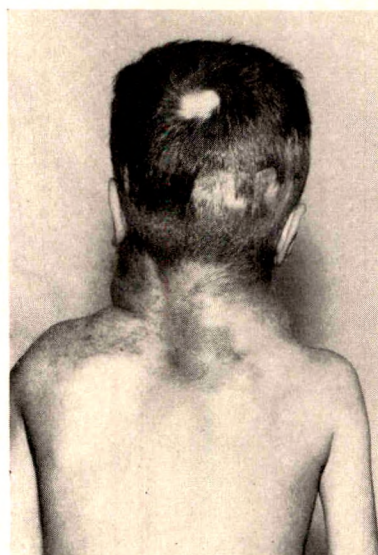


FIG. 10.—Case 3.

logically the condition of the neck was remarkable in that between the trachea and vertebral column there was a mass which had not pushed the trachea forward but had occupied a concavity of the cervical kyphosis as if it were responsible for the condition of the latter (Fig. 11). There had, however, been no specific change in the bones of the cervical vertebrae. An attempt was made to



FIG. 11.—Case 3.

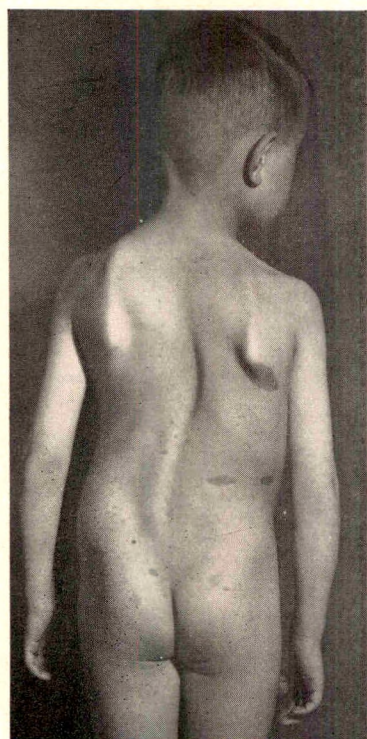


FIG. 12.—Case 4, aged 6 years.

excise the mass at the age of 6 years 1 month but this was unsuccessful. The boy subsequently attended a school for physically handicapped children.

At the age of 15 years his height was $48\frac{1}{2}$ in. (1·21 m.) and his weight 48 lb. (21·8 kg.). He could walk fairly well but did not run. His appetite was good and he went to camp with the scouts.

FAMILY HISTORY. The mother felt on her face and body numerous painless nodules resembling neurofibromata. She remembered that they had appeared after an attack of 'erysipelas' at the age of 16.

Case 4. (Figs. 12-14.) Light brown spots were noticed on the trunk and thighs of this child between the ages of 1 and 3 years. They became more numerous and at the age of 6 years it was noticed that the back was curved.

On examination there were many café-au-lait macules up to the size of 3 cm., mainly on the trunk. There was a mid-dorsal scoliosis with convexity to the right. This could be passively but not actively reduced.

There was a gradual increase in the deformity in spite of orthopaedic treatment.

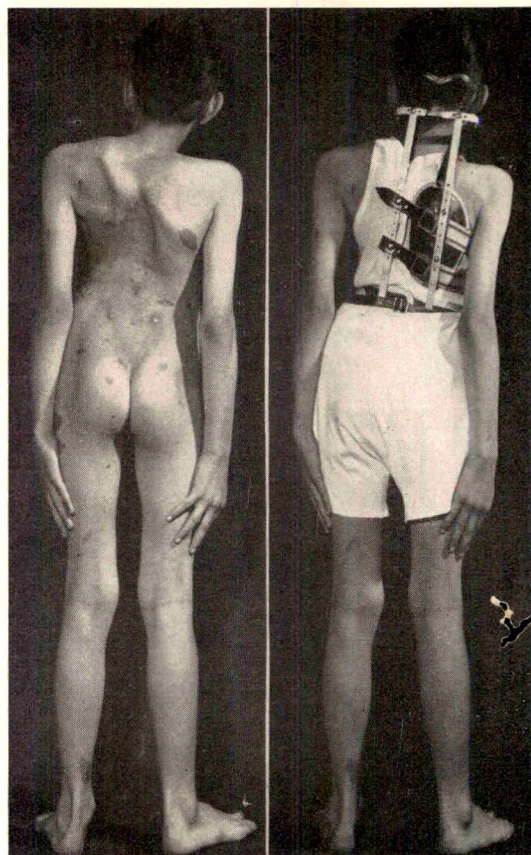


FIG. 13.—Case 4.

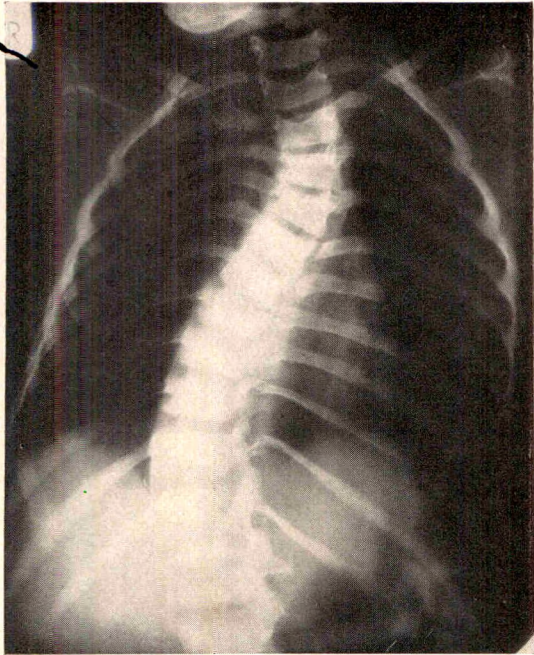


FIG. 14.—Case 4.



FIG. 16.—Case 5, aged 2 years.

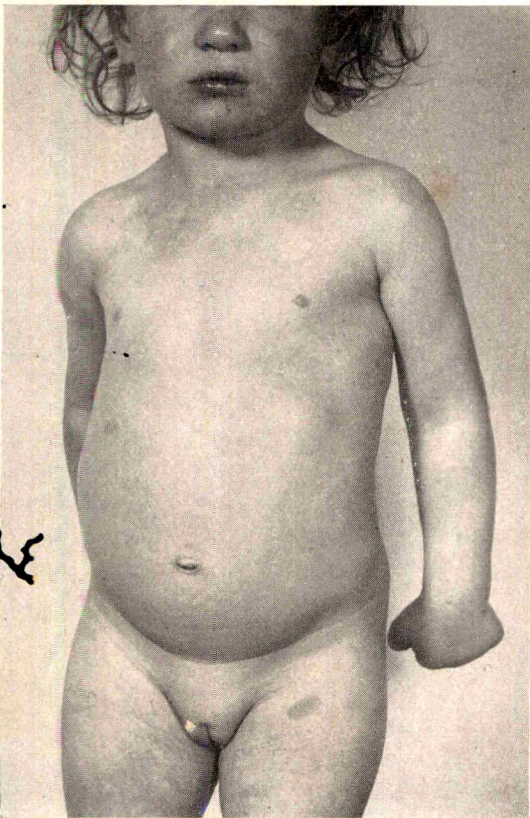


FIG. 15.—Case 5, aged 16 months.

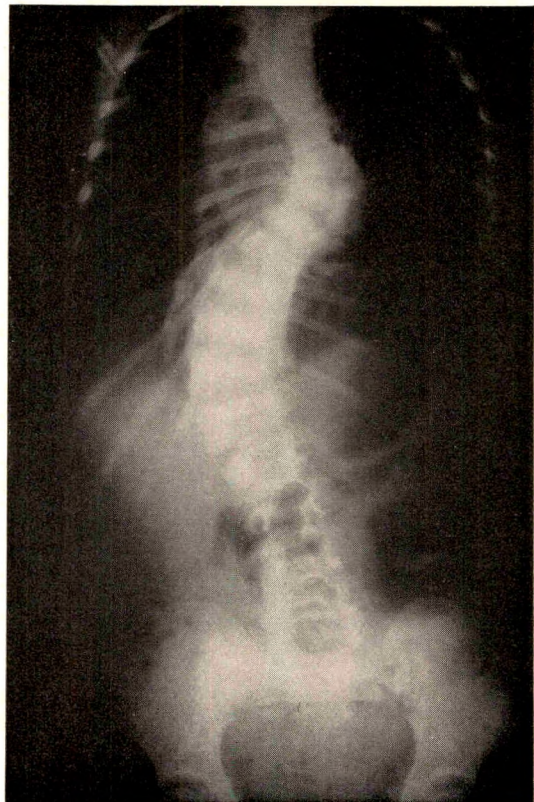


FIG. 17.—Case 5.

FAMILY HISTORY. The father had had brown spots, as had a paternal uncle and the paternal uncle's only daughter.

Case 5. A lump was noticed on the left side of the chest in the region of the nipple when the child was 16 months old (Fig. 15). When she was 2 years old a lump was noticed on the right side of the chest posteriorly (Fig. 16).

Examination at the age of 2 years showed that there was a scoliosis with the upper convexity to the left, the lower convexity to the right (Fig. 17). This largely disappeared when the child was lifted up. Over the trunk several café-au-lait patches were seen ranging from the size of a florin to a pea. No other skeletal deformity was noticed.

There was a gradual increase of the deformity in spite of physiotherapy.

FAMILY HISTORY. The mother was alleged to have been born with, or at all events to have developed shortly after birth, many coloured patches like those on the child. After the patient's birth soft lumps had appeared on her body, too.

Discussion

The changes in the vertebral column are of grave significance. Apart from a tendency to undergo malignant change, the lesions are progressive over

at least several years, reducing the patient to a cripple.

The diagnosis of neurofibromatosis may not be obvious if the skin lesions are minimal. In infancy there may be only one or two café-au-lait spots and several years may elapse before they become more numerous and prominent. While large subcutaneous masses are relatively frequent in infancy, the small polyp so characteristic in the adult is usually absent. The mother of Case 3 remembered that her nodules appeared at the age of 16 following an attack of erysipelas. The mother of Case 5 noticed the 'soft lumps' on her body after the birth of the patient.

In view of the grave prognosis, the diagnosis of neurofibromatosis should be considered in any case of unexplained scoliosis.

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TERATOMA OF THE NECK

REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

BY

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(RECEIVED FOR PUBLICATION JUNE 12, 1959)

Several difficulties were experienced in the diagnosis and management of the two cases which we are reporting. This was due to a lack of detailed knowledge of these tumours, which in turn was due to the absence in the literature of any adequate description of them and especially of their clinical features and treatment; this despite the three reviews which have so far been published (Saphir, 1929; Pusch and Nelson, 1935; Bale, 1950).

It is the object of this paper, therefore, to present a description, gleaned from reviewing the literature and from our own experience, of these tumours, their clinical manifestations and management. The

Definition

Teratomas of the neck are benign cystic, semi-cystic or solid tumours derived from the three germ layers. They are most commonly present in the foetus *in utero*, are sometimes associated with hydramnios and occasionally cause obstruction to labour. The infant may be full-term or premature; it may be stillborn, but is frequently alive at birth. The tumours often cause interference with respiration or swallowing at birth. Sometimes the tumours only become manifest later in infancy or childhood and rarely they may appear in adult life, in which case they are usually malignant.

TABLE 1
SUMMARY OF FINDINGS REVIEWED AND REPORTED BY SAPHIR AND BALE

Author	Sex		Thyroid Tissue				Brain Tissue				Thyroid Gland			'Displacement' of Thyroid Gland				Hydramnios			Operation performed			Thyroid Arteries Entering Tumour		
	M.	F.	No Ref.	Yes	No	No Ref.	Yes	No	No Ref.	Pre-sent	Ab-sent	No Ref.	Yes	No	Doubt-ful	No Ref.	Yes	No	No Ref.	Yes	No	No Ref.	Def-in-ite	Doubt-ful	No Ref.	
Saphir (1929): 29 cases re-viewed; 1 case reported	10	13	7	15	11	4	24	0	6	19	4	7	17	0	6	7	4	12	14	17	13	0	2	3	25	
Bale (1950): 29 cases re-viewed; 4 cases reported	10	9	11	7	18	5	23	2	5	Not mentioned			19	1	2	8	9	8	13	13	17	0	3	0	27	

two case reports illustrate the problems which can arise in dealing with these cases and add to the literature, which is not large.

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The tumours, which appear in the newborn infant and cause interference with respiration and swallowing, present as an urgent matter for diagnosis and treatment. This should not be a difficult problem, as will be shown, and the mortality from excision of the tumour is low provided that surgery

No.	Author and Year	Age	Sex	Race	Thyroid Tissue	Brain
1	Marescot (1945)	15 yr.	N.R.	N.R.	'Follicles with colloid'	N.R.
2	Lantuéjoul and Truffert (1946)	Birth	F.	N.R.	Yes	N.R.
3	Hellmuth (1950)	Birth	M.	N.R.	N.R.	Yes
4	Pozzi (1950)	Birth	M.	N.R.	Yes; near capsule	Yes
5	White and Gosselin (1952)	Birth	M.	White	Yes; near capsule also	Yes
6	McGoon (1952) Case 1	Birth	F.	Negress	N.R.	Yes
7	Case 2	Birth 34 wk prem.	M.	Negro	N.R.	Yes
8	Case 3	? 8 mth.	M.	Negro	'Gland structures in capsule'	Yes
9	Case 4	Birth	M.	N.R.	N.R.	Yes
10	Salviati and Savegnago (1952)	Birth	N.R.	N.R.	N.R.	Yes
11	Perkins and Pautler, (1953)	Birth	F.	N.R.	Yes; in capsule also	Yes
12	Otken (1953)	Birth	M.	N.R.	Yes; beneath capsule	Yes
13	Hinds, Seybold and Walker (1954)	Birth	N.R.	Negro	Yes	Yes
14	Buckwalter and Layton (1954)	28 yr.	F.	N.R.	N.R.	Yes
15	Kresse (1954)	Birth	M.	N.R.	N.R.	N.R.
16	Cavallero (1954)	24 yr.	M.	N.R.	Yes	Yes
17	Malaspina and Somaglino (1955)	Birth	M.	N.R.	N.R.	N.R.
18	Kaminek and Tomik (1957)	Birth 27 wk. prem.	F.	N.R.	N.R.	Yes
19	Salas, Esparza, Angulo and Castañeda (1957)	Birth	F.	N.R.	N.R.	Yes
20	Thomas (1957)	Birth	F.	W. African Negress	N.R.	Yes
21	Silberman and Mendelson (1960) Case 1	Birth	M.	White	Yes	No
22	Case 2	Birth	F.	White	Yes	Yes

is undertaken before deterioration in the condition of the infant has occurred.

Incidence

Saphir (1929) reviewed 29 cases and added one of his own. Bale (1950) reviewed 26 additional cases and added four of his own (Table 1). We have collected 20 previously unreviewed cases (Table 2) which include a case (Marescot, 1945) mentioned but not included in Bale's review (the second case in Marescot's paper is not included because of lack of histological confirmation of the nature of the tumour), a case omitted by Bale (Lantuéjoul and Truffert, 1946) and 18 other cases. There is therefore a total of 82 cases in the literature

to date, including the two reported in this paper.

These tumours are not quite as rare as might be thought when compared with the number of reported cases of teratoma in other sites, e.g. retroperitoneal teratoma (59 cases up to 1949) or mediastinal teratoma (245 cases up to 1945), but these included dermoids and epidermoids as well as teratomas. (These figures are quoted by Gross, 1953.)

Case Reports

Case 1. A full-term white male infant was admitted to Hope Hospital, Salford as an emergency on April 25, 1957, having been born at home three hours earlier. The mother, aged 28 years, had had two previous normal deliveries. Pregnancy in this case was normal; labour

USLY REVIEWED

Thyroid Gland	Hydramnios	Signs and Symptoms	Treatment and Results
	N.R.	N.R.	Operation at 36 yr.; no reference to result
seen; tumour in of gland	Yes	Dyspnoea and apnoea	Operation eighth day; no anaesthetic; died post-operatively
	N.R.	Stridor; cyanosis	Operation at 3 days; post-operative jaundice; well at 2 mth.
seen; tumour in of gland	N.R.	Asphyxia	Died shortly after birth
in	No	Vomiting; dyspnoea	Excision at 3 days; well at 7 mth.
l gland	N.R.	Fever, hoarseness and anorexia at 6 mth.; bronchitis and pneumonia	Treatment of pneumonia died 2 wk. later
half indistinct	N.R.	Cyanosis; weak respiration	Died 1 hr. after birth
	N.R.	Difficult respiration and respiratory infection at 8 mth.	Operation and post-operative tracheostomy; well 3 wk. later
	N.R.	Vomiting; respiratory distress	Caecostomy for imperforate anus; died 2 wk. later
lobe seen	N.R.	Asphyxia; feeding difficulties at birth, then asymptomatic	Operation (local anaesthetic) at 40th day; temporary post-operative paralysis of vocal cord; well thereafter
right lobe	No	None	Excision 6th day; post-operative temporary paralysis of vocal cord; well at 4½ mth.
d to superior pole	No	Increase in size of tumour	Enucleation at 3 wk.; well at 6 wk.
d to thyroid	N.R.	None	Excision at 3 yr.; uneventful recovery
d right lobe and d left	N.R.	Ache; increase in size of thyroid	Total thyroidectomy and radical neck dissection; post-operative radiotherapy and ¹³¹ I treatment; died of metastases 1½ yr. later
	No	Apnoea	Died shortly after birth
	N.R.	N.R.	Excision at 46 yr.
in position of	N.R.	None	Operation at 7½ mth.; no reference to result
absent; tumour t to right lobe	Yes	Apnoea and cyanosis	Died ½ hr. after birth
	N.R.	Cyanosis at birth; dyspnoea; respiratory infection and atelectasis at 6½ wk.	Tracheostomy and cardiac massage at 6½ wks.; died
	N.R.	Slight stridor at 4 mth.	Enucleation-excision at 4 mth.; well 1 wk. later
not seen	No	Dyspnoea and cyanosis at birth	Excision 6 hr. after birth; well at 2 mth.
the left gland	No	Rapid respiration; retained secretions; 'moist' chest	Excision at 4 days; died 2 days later; bronchopneumonia

lasted approximately 10 hours and was reported by the midwife in attendance as having been uncomplicated. Both parents were healthy and there were no known familial diseases.

The infant, who was well developed, was extremely ill with very rapid respiration which was 'grunting' in character; there was deep cyanosis and marked rib recession; the heart and lungs were normal. The rest of the general examination was negative.

EXAMINATION OF NECK (Figs. 1 and 2). There was a spherical tumour about 7.5 cm. in diameter situated on the left side of the neck extending from the parotid region above to the clavicle below and from over the mid-line medially well into the posterior triangle. It was hard, without any cystic areas, and its surface was bosselated. The skin over the surface of the tumour

was freely mobile. On its deep surface the tumour appeared to have some attachment in the vicinity of the larynx and thyroid gland but was only loosely attached elsewhere so that the entire tumour was mobile in all directions and hung down over the anterior chest wall because of its weight. The left pinna was displaced upwards and the left half of the body of the mandible appeared to be displaced upwards. The larynx and trachea were obscured by the medial border of the tumour.

The infant was placed in an incubator and given continuous oxygen with some improvement but soon became again deeply cyanosed and limp and appeared to be moribund. Coramine 0.5 ml. and eucortone 0.5 ml. were given intramuscularly and oxygen was given by face mask with marked improvement, but the respiration nevertheless remained difficult and cyanosis persisted.



FIG. 1.

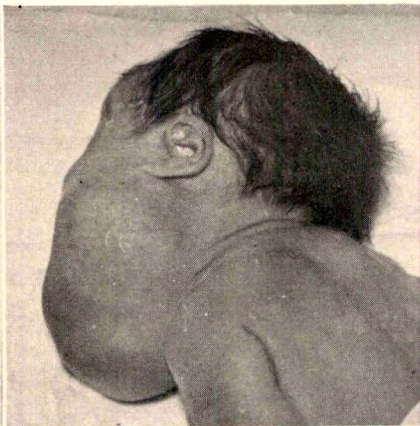


FIG. 2.

FIGS. 1 and 2.—Case 1.
Lateral views of tumour.

A radiograph of the neck (Fig. 3) showed the presence of a soft tissue tumour on the left side of the neck; there was no calcification of the tumour. The trachea was compressed antero-posteriorly; the left half of the mandible showed an absence of the normal angle between body and ramus and these two formed a straight line from the symphysis menti to the base of the skull. The chest was normal.

Tracheostomy was not possible because the tumour overlapped the midline. Excision of the tumour appeared to offer the only possible chance of success. A tentative pre-operative diagnosis of congenital malignant tumour was made.

OPERATION. This was undertaken about three hours after admission under general anaesthesia with endotracheal intubation. A curved skin incision was made, medial and lateral skin flaps were raised and the tumour

was dissected out of its bed with ease because of the well defined capsule and the lack of attachment except in the vicinity of the larynx and thyroid gland, where careful dissection was necessary. It was not possible to ascertain whether the blood supply of the tumour originated in the thyroid arteries or not. No attempt was made to identify the thyroid gland. Haemorrhage during the operation was minimal. The wound was closed with interrupted skin sutures and a Penrose drain was brought out through the wound. The operation was well tolerated.

The drain was removed after 48 hours and the skin sutures on the eighth post-operative day. There were no respiratory difficulties except for stridor, which appeared if the infant was disturbed. Cyanosis did not recur.

The infant was discharged after three and a half weeks

FIG. 3.—Case 1. Lateral radiograph showing soft tissue shadow, compression of trachea and absence of angle of left mandible.



FIG. 3.



FIG. 4.

FIG. 4.—Case 1. Post-operative view of neck.

in hospital (Fig. 4), having gained weight progressively. The wound was well healed, breast feeds were being taken normally and there were no respiratory difficulties.

The infant was asymptomatic and healthy when seen at follow-up two months later.

APPEARANCE OF GROSS SPECIMEN. This was an almost spherical, solid tumour measuring $7.5 \times 6.5 \times 6.5$ cm.

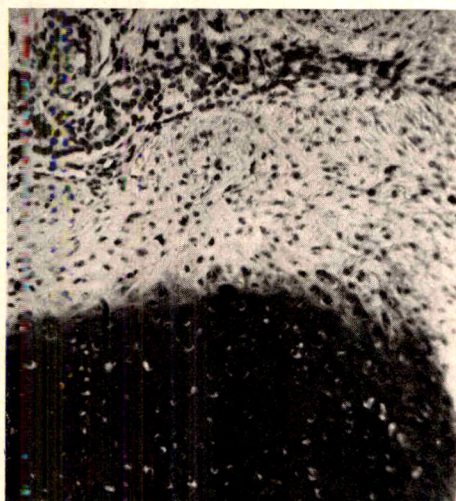


FIG. 5.—Case 1. Photomicrograph showing cartilage in its lower half.

It was greyish-white in colour and the surface was irregular and lobulated. The tumour was well encapsulated.

The cut surface was firm and fibrous with scattered areas of what appeared to be cartilage.

MICROSCOPICAL APPEARANCE (Figs. 5 and 6). Dr. G. J. Crawford (Hope Hospital) reported:

'The tumour is well circumscribed and in places has a thin fibrous capsule from which fibrous trabeculae run inwards. In several places compressed thyroid tissue is present in the capsule; groups of thyroid acini are also seen in the tumour, strands of epithelial cells and a small island of squamous cells. About half the tumour is composed of fairly cellular fibrous tissue, about one-third of cartilage and the remainder of small areas of myxoid tissue and fat. There is one small area of undifferentiated mesenchyme in which two mitoses were observed. In many of the sections there are scattered foci of haemopoiesis; some of these are associated with fat and thin-walled blood vessels as in bone marrow. The tumour is well supplied with blood vessels, mostly capillaries. No nerve tissue was found. All the tissues in the tumour are either found normally in this area or could be formed from the local mesenchyme. I consider that it is a malformation (hamartoma).'

The tumour was shown to the Children's Tumour Registry of the University of Manchester whose panel of pathologists kindly examined the sections. Their reports and comments are, with their kind permission, given below.



FIG. 6.—Case 1. Photomicrograph showing thyroid follicles.

Professor A. C. P. Campbell (University of Manchester):

'Either a teratoma or a mixed tumour of ectopic tracheo-bronchial anlage. I think it is more probably the latter; all the tissue elements present are compatible with a tracheal origin (explaining the squamous epithelium as metaplastic). It appears benign.'

Dr. Agnes R. Macgregor (Royal Hospital for Sick Children, Edinburgh):

'The tumour is composed of a mesoblastic tissue among which are many masses of cartilage. The mesoblastic tissue varies in character from a moderately cellular collagenous tissue to virtually undifferentiated mesenchyme, in which mitoses are numerous; there are also myxomatous areas. There are atrophied thyroid vesicles at the periphery and epithelial acini, probably of thyroid tissue, appear here and there in the substance of the tumour. No other varieties of tissue are identified.

Inference: It may be a teratoma, but as the epithelial elements appear to be thyroid tissue and all the other elements are mesoblastic, it seems to fit very well the description of the "mixed tumour of the thyroid" mentioned by Willis in *Pathology of Tumours*, 1948, p. 616. The less differentiated parts are histologically malignant.'

Dr. H. Marsden (Royal Manchester Children's Hospital):

'There is loose mesenchymal tissue with spindle cells and numerous islands of cartilage. In addition follicles lined by cuboidal epithelium and containing eosinophilic material are noted. The latter resemble thyroid follicles. The picture is that of a benign teratoid tumour.'

Dr. H. Russell (Christie Hospital, Manchester):

'A defined mass of anomalous mesenchyme in which well-formed cartilage is conspicuous. There appears to be a rim of thyroid tissue closely applied to its periphery. An anomaly of development of the branchial arches.'

R. A. Willis (Prof. Emeritus, University of Leeds):

'A most unusual tumour, composed of moderately cellular vascular mesenchyme with many areas of chondrification, in which some thyroid vesicles and tortuous epithelial strands are incorporated. Thyroid tissue is also present around its well-defined margin. The two possibilities are (I) teratoma, and (II) a chondromatous hamartoma of the thyroid; because of the incorporation of thyroid tissue, I incline to (II). But further sections should be made, in search of other teratomatous tissues. In my opinion the growth is probably benign.'

Even though no uniformity of opinion has been expressed by the panel of pathologists, many of them classified the tumour as a teratoma. For this reason and also because of the extremely close resemblance, both clinically and pathologically, of this tumour to the cases previously reported in the literature as teratoma of the neck, it has been thought quite justifiable to classify it as such.

Case 2. A full-term white female infant was admitted to Memorial Hospital, New York, on June 28, 1949, having been born elsewhere 21 hours previously. The mother, a 28-year-old primipara, had persistent nausea throughout the pregnancy which was otherwise uneventful. Labour lasted 20 hours and the infant was delivered by mid-forceps because of a persistent occipito-posterior position. The weight at birth was 7 lb. 4 oz. The infant had required suction of the mouth and pharynx at birth because of an accumulation of secretions; she had vomited fluids given to her by mouth.

The infant was well developed and was in mild distress from accumulated secretions in the pharynx. Respiration was 44 per minute, heart rate 144 per minute and temperature 99° F. There were numerous rhonchi in the left lung anteriorly. The rest of the general examination did not reveal any other significant findings.

EXAMINATION OF NECK (Figs. 7 and 8). There was a firm, rounded, mobile mass about 14 cm. in diameter situated in the left side of the neck. It extended from the midline of the neck into the posterior triangle; superiorly it extended onto the face and reached the level of the external auditory meatus. Inferiorly, it extended



FIG. 7.—Case 2.
Anterior view of tumour.



FIG. 8.—Case 2.
Lateral view of tumour.

to the root of the neck. The head was displaced to the right. There were a few dilated vessels on the surface of the mass. The anterior part of the mass appeared to be cystic but the rest of the tumour was solid.

INVESTIGATIONS. A blood count and chemical and microscopical examinations of the urine were normal.

A chest radiograph was normal.

A radiograph of the neck (Fig. 9) showed that the tumour contained multiple areas of calcification; the trachea, larynx and oesophagus were normal.

The tumour was aspirated and found to be multicellular; 50 ml. of sero-sanguinous fluid was obtained.

The infant took glucose feeds but vomited frequently; her weight dropped to 6 lb. 6 oz. There were periods of

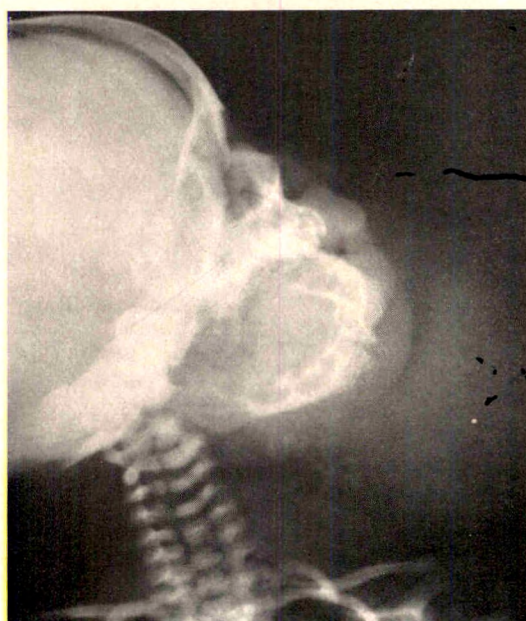


FIG. 9.—Case 2. Lateral radiograph showing calcification in tumour.

cyanosis and difficulty with respiration, which required frequent suctioning. It was decided that an emergency operation would be necessary. The pre-operative diagnosis was between cystic hygroma, branchial cleft cyst and dermoid cyst.

OPERATION (JULY 1, 1949). Without anaesthesia, an H-shaped incision was made and the tumour was dissected from its bed and removed with its capsule intact. The origin of the blood supply of the tumour was not accurately identified and the thyroid gland was not visualized. The skin was approximated with fine nylon sutures and a Penrose drain was brought out from the wound. The operation was well tolerated.

The infant was placed in a steam tent with oxygen and was given injections of penicillin. She was given tube feeds because she was unable to take oral feeds, but some regurgitation occurred. Thirty-six hours post-operatively her temperature rose and she developed massive consolidation (or collapse) of the left lung and bronchopneumonia of the right lung. Her condition deteriorated rapidly and she died on the second post-operative day.

AUTOPSY (JULY 4, 1949). This showed that death was due to bilateral severe broncho-pneumonia with abscess formation; aspirated material was present in a few of the bronchi. The thyroid gland, which was grossly normal, was removed and found to be histologically normal.

projected a mass measuring $5.5 \times 5 \times 4$ cm. The lining of the cyst was grey to grey-tan in colour and contained a few yellow-grey plaques up to 3 mm. in diameter. The sectioned surface of the mass was made up of innumerable tiny thin-walled cysts measuring from 1-10 mm. in diameter. These cysts contained clear mucoid material. Scattered throughout the mass were areas of calcification up to 8 mm. in diameter.



FIG. 11.—Case 2. Cut surface of tumour.

MICROSCOPICAL APPEARANCE (Figs. 12-14). The tumour was found to be a benign teratoma which



FIG. 10.—Case 2. Operative specimen. Note excellent capsule.

APPEARANCE OF GROSS SPECIMEN (Figs. 10 and 11). A well-encapsulated, grey-tan rounded tumour measuring $7.5 \times 6.5 \times 5.5$ cm. was found on section to consist of a large cystic cavity containing bloody fluid into which



FIG. 12.—Case 2. Photomicrograph showing choroid plexus.

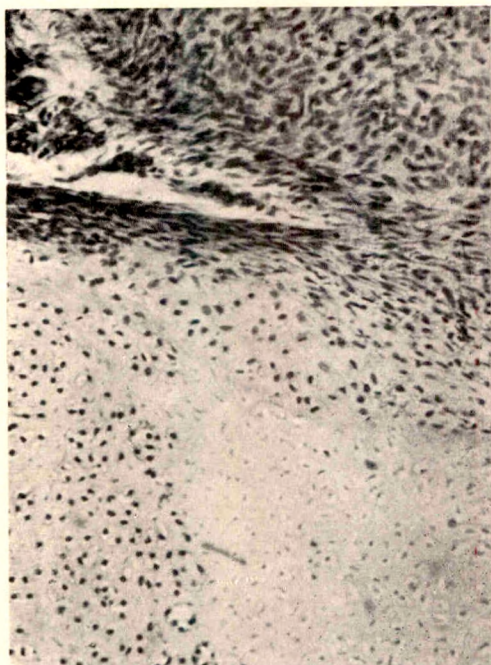


FIG. 13.—Case 2. Photomicrograph showing cartilage.

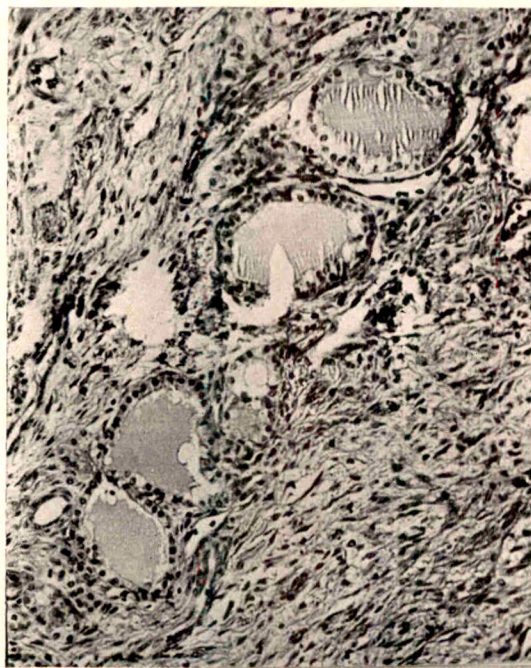


FIG. 14.—Case 2. Photomicrograph showing thyroid follicles.

contained cysts lined with squamous, cuboidal or columnar epithelium; other cysts contained papillary projections. Bronchial epithelium, smooth muscle, immature cartilage and embryonic connective tissue were identified. Thyroid follicles and brain tissue (nerve fibres, glia, choroid plexus) were also in evidence.

Discussion

Nomenclature. Attempts have been made in the past to define which tumours should be called teratoma of the thyroid gland and which should be called cervical teratoma.

Saphir (1929) stated that if the thyroid gland was absent the tumour was a thyroid teratoma, but that if the thyroid gland was present the tumour was a teratoma of the neck. These criteria, we think, are basically sound but require further elaboration and clarification.

Bale (1950) disagreed with Saphir's method of classifying the tumours and instead proposed a more complicated nomenclature, viz. (a) teratoma of the thyroid gland if the thyroid arteries supplied the tumour; (b) teratoma of the neck in the region of the thyroid gland if the tumour replaced all or part of the gland; and (c) teratoma of the neck, probably in the region of the thyroid gland, because of the general appearance of the tumour. This classification suffers from several objections. Firstly, the fact that the thyroid arteries supply the tumour cannot be accepted as evidence that the tumour has its origin in the thyroid gland; these arteries supply many structures other than the thyroid gland and a tumour supplied by them may have arisen from any one of these structures, e.g. parathyroids, larynx, soft tissues. Secondly, very few reports in the literature mention the blood supply of the tumour and hence are unclassifiable on Bale's criteria. Thirdly, in carrying out an emergency procedure for a cervical teratoma on a newborn infant, it would be extremely unwise to search for the thyroid arteries if they were not easily visible (this obviously does not apply to autopsy specimens). Finally, the creation of three categories of tumour, as proposed by Bale, appears cumbersome and unnecessary.

We propose that the tumour be referred to as a cervical teratoma unless it fulfills the following criteria, in which case it may be called a true teratoma of the thyroid gland. The teratoma is situated in the position of the thyroid gland and in addition (a) the thyroid gland is present and the tumour occupies a portion of it; or (b) the thyroid gland is only partially present, but the tumour is in direct continuity with it, the two forming one mass; or (c) the thyroid gland is completely absent and the tumour replaces the gland entirely.

When a teratoma is adjacent to, but not in direct continuity with, a thyroid gland which may be only partially present, then the tumour cannot be classified as a true teratoma of the thyroid gland because the tumour may well have arisen outside the gland and given rise to atrophy of the gland by pressure.

The presence or absence in the tumour of thyroid tissue is of no particular value in classification since by their very nature all teratomas are capable of producing a wide variety of tissues, and thyroid tissue is no exception.

Accordingly the following cases which have appeared since 1945 should be referred to as true thyroid teratomas: Cases 2, 4, 12, 14, 17 and 18 (see Table 2), possibly Cases 5 and 13 (see Table 2) and Bale's (1950) first three cases.

Age. The age distribution in 79 of the 82 cases reported to date in which age is mentioned is seen in Fig. 15.

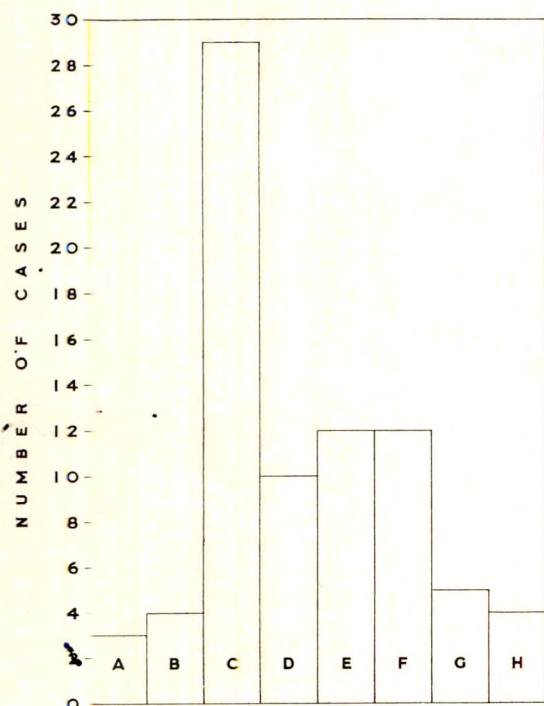


FIG. 15.—Age distribution of 79 cases.

- A = live premature infants
- B = stillborn premature infants
- C = live full-term infants
- D = stillborn full-term infants
- E = birth to 1 month
- F = 1 month to 1 year
- G = 1 year to 15 years
- H = adults

Neither Saphir's (1929) nor Bale's (1950) reviews state whether they refer to the date of appearance of the tumour or the age of the patient when first seen. Nevertheless, it can be presumed that most, if not all, of the cases up to 1 month old and many of those up to 1 year old had the tumour at birth. In those cases which we have collected we have taken care to utilize the age at appearance of the tumour and not the age of the patient when first seen.

In any case, it can be seen from Fig. 15 that the majority of tumours were present at birth although some do not appear to present until later. The tumour is rare after the age of 1 year.

Sex. The sex of the patient was mentioned in 61 cases out of 82 in the literature, of which 30 were females and 31 were males.

Race. Although most of the tumours have appeared in white patients, they have also been reported in Negroes (Saphir, 1929; McGoon, 1952; Hinds, Seybold and Walker, 1954; Thomas, 1957).

Histology. All varieties of tissue from the three germinal layers have been found in these tumours. Particular mention has been made in the past of brain tissue, which has been observed in 47 of 60 cases of Saphir's and Bale's and in 17 of our 22 cases, and also of thyroid tissue, which was present in 22 of Saphir's and Bale's 60 cases and in 11 of our 22 cases (see Tables 1 and 2).

The vast majority of tumours were benign on histological examination but, unfortunately, there has been no long-term follow-up on them. Four definite cases of malignancy have been reported to date. Three were mentioned by Bale (1950). The first was a 9-week-old infant, who died on the day of operation (Pupovac, 1896). The second was a 53-year-old woman, who died of metastatic pulmonary sarcoma from probable malignant proliferation of the teratoma (Lurje, 1908). The third was a 41-year-old female, who died one month post-operatively of widespread metastatic sarcoma, probably originating in the teratoma (Fritzsche, 1920). The fourth case was reported in 1954 by Buckwalter and Layton. Their patient was a 28-year-old female, who died of metastases 15 months after total thyroidectomy and radical neck dissection. The tumour had caused progressive enlargement of one lobe of the thyroid gland for a period of six months prior to surgery. On histological examination it was found to have contained immature neural tissue and muscle as well as cartilage, mesenchyme and gland structures.

Signs and Symptoms. The following remarks are based on a close study of all the cases reported since

1945 (see Table 2) and therefore include Bale's (1950) four cases.

The majority of tumours were oval in shape; an occasional one was spherical. In size, except for Cavallero's (1954) case, in which the tumour was the size of a nut, most of the tumours were between 5 cm. and 12 cm. in their longest axis. When compared with the antero-posterior diameter of a newborn infant's head, which is 10 cm. (approximately), it can be appreciated that these tumours are quite large.

Most of the tumours were situated on one or other side of the neck, usually extending up as far as the mastoid process and body of the mandible and often displacing the lobule of the ear upwards; many tumours reached the zygomatic arch. Posteriorly they usually reached the anterior border of trapezius and anteriorly they often crossed the midline for a short distance. The inferior border of the tumour was most frequently the clavicle but in two cases the tumour entered the mediastinum (Salas, Esparza, Angulo and Castañeda, 1957; Kaminek and Tomik, 1957). In four cases (Lantuéjoul and Truffert, 1946; McGoon's third case, 1952; Pozzi, 1950; Malaspina and Somaglino, 1955) the tumour was situated in the position of the normal thyroid gland and was mistaken for a congenital goitre. The tumour reported by Buckwalter and Layton (1954) was the only one which was palpated as a swelling in a lobe of the thyroid gland; but this tumour occurred in an adult aged 28 years who had a malignant teratoma.

The consistency of the tumour varied. It was cystic, or partly solid and partly cystic, or entirely solid. However, in most instances fluctuant cystic areas were palpable. An occasional case was transilluminated. The surface of the tumour was usually irregular, being described as lobulated, bosselated or loculated, and the borders of the tumour were usually well defined.

In only a few case reports was the mobility of the tumour mentioned. In these cases the tumour was usually quite mobile as was the skin on the surface of the tumour. A few reports mentioned that there were collateral veins on the surface of the tumour.

The cases which were not stillborn usually had acute symptoms at birth. These were cyanosis, dyspnoea, apnoea and stridor due to tracheal deviation and/or tracheal compression. In a few instances swallowing difficulties occurred. These symptoms often led to a fatal termination if early treatment was not undertaken (McGoon, 1952; Kaminek and Tomik, 1957). Occasionally, the infant was asymptomatic at birth and only several weeks or months later developed serious symptoms (McGoon, 1952; Salas *et al.*, 1957) and in a few

instances the tumour remained entirely asymptomatic (Otken, 1953; Hinds *et al.*, 1954).

The presence and degree of tracheal deviation and obstruction was often demonstrable radiologically. The radiograph also showed calcification of the tumour in a few cases, as occurred in our second case, in McGoon's (1952) fourth case and in Thomas's (1957) case.

Aspiration of the mass was performed in the case described by Lantuéjoul and Truffert (1946). They obtained opalescent fluid but were not able to empty the cyst of its contents, indicating its multilocular nature. Our second case was aspirated and sero-sanguinous fluid was obtained; aspiration also showed that the tumour was multilocular.

Effects of Tumour on Pregnancy and Labour.

There have been two cases of hydramnios in the cases reported since 1945 (Lantuéjoul and Truffert, 1946; Kaminek and Tomik, 1957). Before 1945 13 cases had been reported (Table 1), making a total to date of 15 instances in 82 case reports (18%). This coincides well with the high incidence of hydramnios which is known to occur in cases of foetal malformation. Hydramnios is often associated with anomalies such as oesophageal atresia, in which the foetus is unable to swallow the liquor amnii. This is postulated as an aetiological factor in hydramnios (Eastman, 1956). It is possible that the oesophageal obstruction produced by a cervical or thyroid teratoma is in a similar manner responsible for the high incidence of hydramnios in these cases.

The size of the tumour may impede labour and may require the application of forceps (White and Gosselin, 1952; Kresse, 1954; our second case) or caesarean section (Salviati and Savegnago, 1952) or episiotomy (Perkins, Pautler and Winston-Salem, 1953). In the case reported by Salviati and Savegnago (1952) the tumour was stated to have been palpated in the abdomen and per vaginam.

Associated Congenital Anomalies. Two instances of associated congenital anomalies have appeared since 1945: 'chondro-dystrophia foetalis' was present in McGoon's (1952) second case and imperforate anus in his fourth case.

Differential Diagnosis. Some of the diagnoses, which have been considered by various authors pre-operatively, are cystic hygroma, congenital goitre, branchial cyst, lymphangioma, simple multilocular cyst, dermoid cyst, neuroblastoma, parotid tumour and carcinoma of the thyroid gland (in Buckwalter and Layton's case of malignant teratoma in an adult).

The chief tumours which require differentiation are cystic hygroma, congenital goitre and branchial cyst.

In age incidence, sex incidence, site, size and surface of the tumour, teratoma and cystic hygroma are similar. However, a cystic hygroma usually has a limpid consistency and poorly defined borders and is easily transilluminated (Gross, 1953); teratomas are often tense or solid in consistency, have well defined borders, are usually freely mobile and only occasionally can they be transilluminated. Radiography may demonstrate calcification in teratomas but not in hygromas. Finally, hygromas produce few symptoms, except when infected or very large, which is in direct contrast with the respiratory and feeding difficulties commonly seen with teratomas.

In those instances in which the teratoma occupies the position and has the shape of a thyroid gland it must be differentiated from a congenital goitre. However, since congenital goitres are rare outside endemic areas (McQuarrie, 1957), the problem is practically limited to these areas. Radiography of the neck may be of value in demonstrating the presence of calcification in a teratomatous tumour.

The following features of a branchial cyst serve to differentiate it from a teratoma: it is commonest in the third decade and presents as a smooth, globular swelling deep to the anterior border of the sternomastoid muscle, usually at its middle; on aspiration typically it yields a milky fluid containing cholesterol crystals (Aird, 1957).

Prognosis and Treatment. Forty-six patients of all those reported thus far (82) have undergone surgery, and seven died. Of the deaths, three occurred in patients with malignant tumours: one was an operative death, the second was an adult who died of metastases (both mentioned by Bale, 1950) and the third was also an adult who died of metastases (Buckwalter and Layton, 1954). Of the remaining four deaths one was an infant who died of cardiac arrest due to an attempted tracheostomy (Salas *et al.*, 1957) and another was our second case who died of broncho-pneumonia post-operatively. According to Bale (1950), the cause of death was not mentioned in the remaining two cases. The mortality with surgical treatment is thus about 9% if the malignant tumours are not included, an extremely low figure considering that over half the cases were treated before 1930.

Of the 36 cases in which surgery was not undertaken, 14 were stillborn and one was an adult who died of metastases from a malignant tumour (Bale, 1950). The remaining 21 cases were live, newborn

infants, all of whom died without having had any operative treatment. It is difficult to estimate how many of these infants could have been saved by surgery but, to mention a few instances only, the lack of early surgical treatment was most probably responsible for death in two of McGoon's (1952) cases and in Carter's case (mentioned by Bale, 1950).

Thus the significant facts are that the mortality from operation on benign cases at all ages is low; that more than 25% of all patients died soon after birth without having had surgery; that it is more than likely that many of these infants could have been saved by timely operation.

Hence the first principle in the treatment of these tumours in infants is early operation, especially when tracheal and oesophageal obstruction are present. Delay in surgery, when the respiratory passages are partially obstructed, leads to retention of secretions, atelectasis and broncho-pneumonia. When the tumour does not encroach on the trachea or oesophagus surgery may be postponed, but this is not common.

In the pre-operative phase resuscitative measures such as tracheal aspiration, oxygen and stimulants may be required; laying the infant on the side of the tumour may help to relieve some of the compression and traction on the trachea.

The operation should consist of excision of the tumour and its capsule together with redundant skin. General anaesthesia with intubation should be employed; some authors have employed local anaesthesia (Salviati and Savegnago, 1952) or no anaesthesia at all (Lantuéjoul and Truffert, 1946).

In benign cases, the operation itself is relatively simple since the tumour 'shells out' without much difficulty. Care should be taken when the tumour is loosely adherent to the respiratory passages or thyroid gland since temporary vocal cord paralysis has occurred (Salviati and Savegnago, 1952; Perkins and Pautler, 1953). Caution may be required when, occasionally, the tumour enters the mediastinum.

Tracheostomy without excision of the tumour is not usually possible since the tumour obscures the trachea in many cases. However, tracheostomy has been performed after removal of the tumour (Lantuéjoul and Truffert, 1946; McGoon, 1952) in order to establish and maintain a patent airway.

Post-operatively, meticulous care should be taken in maintaining a patent airway; antibiotics should be given and oral feeding may be carefully commenced fairly soon after surgery. When the thyroid gland is absent or is removed by operation replacement therapy with thyroid extract will be required.

It is not proposed to discuss the management of

malignant teratoma in detail. However, wide local excision of the tumour is obviously mandatory if there is to be any prospect of avoiding local recurrence.

Summary

Cervical teratomas have been defined. Twenty-two new cases have been added to the 60 cases previously reviewed. Two personal cases have been described in detail.

Previous attempts to distinguish thyroid from cervical teratoma have been indicated and a new set of criteria proposed. The tumours usually appeared at birth and were equally divided between the sexes. Several cases have been reported in Negroes.

Histologically tissues from all the germinal layers were found including brain and thyroid tissue. Except for four cases of malignancy (three in adults) all the tumours were benign.

The appearance of the tumour has been described in detail and the likelihood of acute obstructive symptoms of the larynx and oesophagus at birth has been indicated. The tumour caused hydramnios in 18% of cases and occasionally impeded labour. Occasionally congenital anomalies were present in other parts of the body.

The chief points in differentiating the tumour from cystic hygroma, congenital goitre and branchial cyst have been indicated.

The mortality with surgery in benign cases was 9%. On the other hand, all cases not treated surgically died. The principles of surgical treatment have been outlined.

We would like to thank Mr. George Brown and Dr. R. I. Mackay of Salford for permission to publish the first case and Dr. J. K. Steward of the Manchester Tumour Registry for help with the pathological data in that case. We also wish to thank Dr. Harold Dargeon of New York for permission to publish the second case.

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Addendum

Since this paper was written an article has appeared reporting two further cases of teratoma of the neck (Keynes, W. M. (1959). Teratoma of the neck in relation to the thyroid gland. *Brit. J. Surg.*, 46, 466). A summary of tumours reported since 1950 is given, but omits mention of Cases 1-4, 10 and 15-19 (see Table 2). It provides reference to two cases before 1950 which we had omitted (Shattock, S. G. (1882). Congenital tumour of the neck. *Trans. path. Soc. Lond.*, 33, 289; Daniels, D. W. (1928). Congenital tumour of the neck. *Brit. J. Surg.*, 15, 523).

AMOEBIC LIVER ABSCESS IN AFRICAN CHILDREN

BY

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Amoebiasis is common among Africans in Durban, where this hospital alone handles over 2,500 patients each year. Children share in this high incidence of the disease. Many cases are severe and liver abscess is frequently seen.

The purpose of this paper is to compare and contrast the features of amoebic liver abscess in children with those in adults and to discuss clinical diagnosis.

Material

This consists of a series of 53 cases of amoebic liver abscess admitted to the Paediatric Department during a period of seven years from November, 1951. All were proved by demonstration of pus either by aspiration or at necropsy.

Age Incidence. The age distribution is shown in Fig. 1. The youngest was 8 weeks and the oldest 5 years. Seventeen were under 1 year, 10 being less than 6 months old.

Senecal, Larivière, Dupin and Trenou (1957), in reporting four cases of amoebic liver abscess in children, state that Lestrade and Guérineau had found that up to 1956 the world literature contained only 47 reported cases of amoebic liver abscess in children. Since then Torroella, Lopez and Villareal (1956) have described 14 cases in children under 6 years in Mexico.

Although this condition is uncommon in children elsewhere, it is not infrequently seen in African children in Durban.

Sex Distribution. Thirty-two of the 53 cases were males. Torroella *et al.* (1956) described 14 cases in children, of whom 5 were males. It appears that male predominance is less in children than in adults.

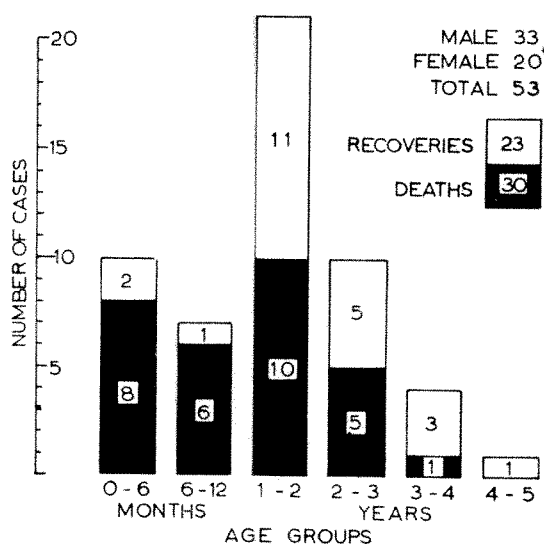


Fig. 1.—Amoebic liver abscess in children. Age incidence and outcome of 53 cases.

Location of Abscesses. The location of abscesses clinically and at necropsy was as follows:

Right lobe	33 (62%)
Left lobe	2 (4%)
Central at junction of lobes of liver	5 (9%)
Multiple	13 (25%)

Abscesses are said to be characteristically single and to occur most often in the right lobe. In this series 75% were single and 25% multiple (Fig. 2). These figures show that the distribution of single abscesses is similar to that reported elsewhere. It seems that multiple abscesses are commoner in Durban African children than is usually the case,

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but this may be due to the high proportion of necropsies.

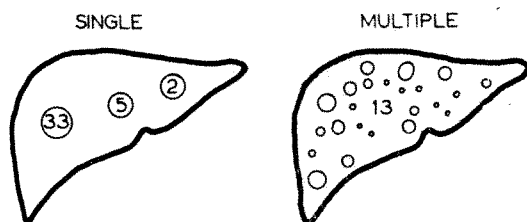


FIG. 2.—Location of amoebic liver abscesses in 53 cases.

Fever. This was present in all cases (Fig. 3). The temperature usually fluctuated between 102 and 103° F. until appropriate therapy was begun. In adults fever is not a constant manifestation of liver abscess (Wilmot, 1949; Lamont and Pooler, 1958). In children, however, it is an important and striking feature.

was observed in 34 cases, and between 30,000 and 43,000 W.B.C.s per c.mm. in six others. Two fatal cases with extremely high counts were found to have single hepatic lesions at autopsy. Three with very high counts recovered and the two lowest counts of 8,000 and 9,000 occurred in children who at autopsy had multiple lesions. These findings do not confirm the opinion that a pronounced leucocytosis indicates multiple abscesses with a bad prognosis (Rogers, 1922).

My findings show that in children the white cell count is more often raised and the elevation is greater than in adults, in whom leucocytosis is present in only 70-80% (Wilmot, 1949; Lamont and Pooler, 1958).

In these children the duration of the history bore no relationship to the level of the white cell count, unlike the findings of Lamont and Pooler (1958).

A normocytic normochromic anaemia was present in 38 cases, the haemoglobin being 7.6 g./100 ml. (range 4.8 to 10.0 g./100 ml.). Anaemia is an important feature of the disease in children and

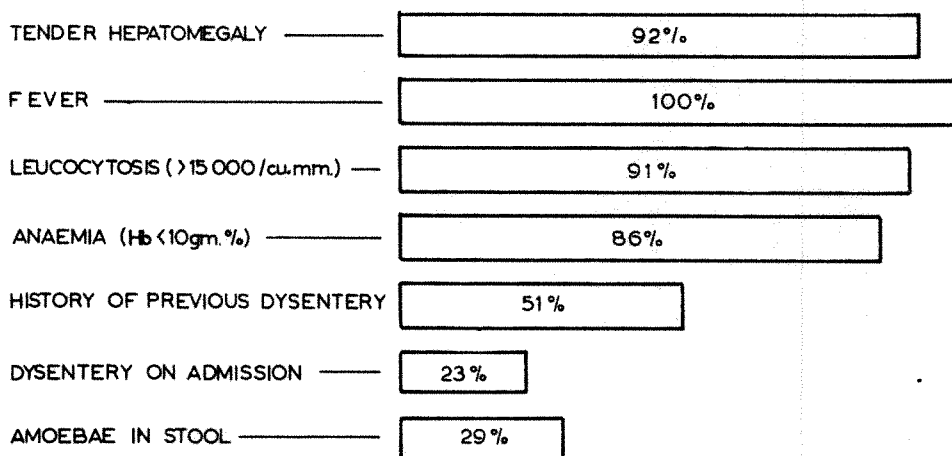


FIG. 3.—Incidence of common clinical findings in 53 cases of amoebic liver abscess.

Tender Hepatomegaly. This was present in all but four cases. It is unusual for the liver not to be enlarged to at least three fingers' breadth below the costal margin. Intercoastal tenderness may be difficult to elicit in infants but direct palpation of the liver is usually exquisitely painful. A palpable mass was present in 40.

Haematological Findings. Blood examination was done in 44 cases. The white blood cell count was raised in 40 (91%). In the remaining four it ranged from 8,000 to 11,000 W.B.C.s per c.mm. Leucocytosis between 15,000 and 29,000 W.B.C.s per c.mm.

rapidly improves with treatment of the primary disease.

Radiological Findings. Radiological examination of the chest was done in 35 cases; 11 (31%) showed elevation of the diaphragm, seven of these having associated pulmonary changes. Figs. 4a and b and 5a and b show the radiological changes in two cases. It seems that radiology is less often helpful in children than in adults, among whom the majority exhibit diaphragmatic elevation (Ochsner and DeBailey, 1943; Wilmot, 1949; Lamont and Pooler, 1958).

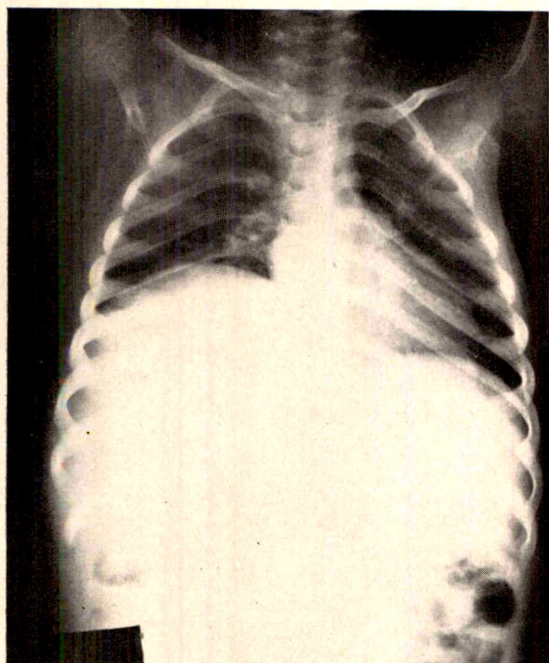


FIG. 4a.

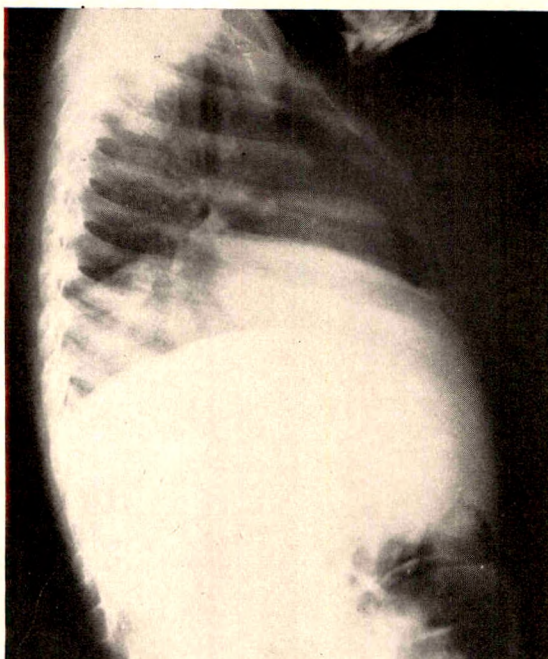


FIG. 4b.

FIG. 4 (a and b).—Radiographs of chest showing marked elevation of right dome of diaphragm before aspiration of large liver abscess (total of 926 ml. of pus removed).

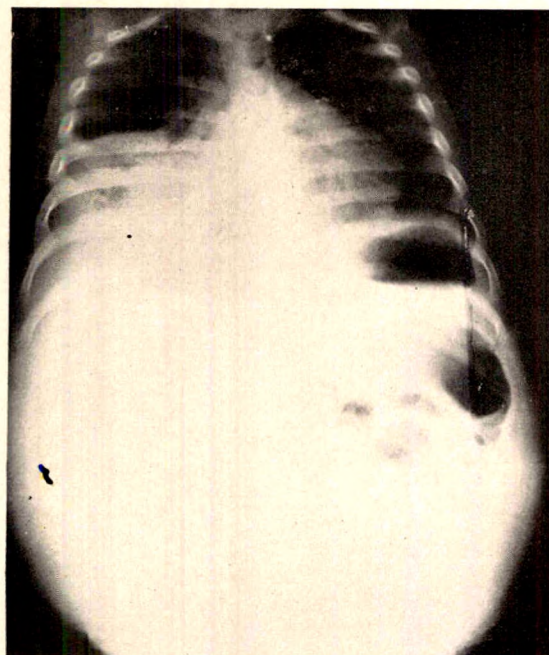


FIG. 5a.

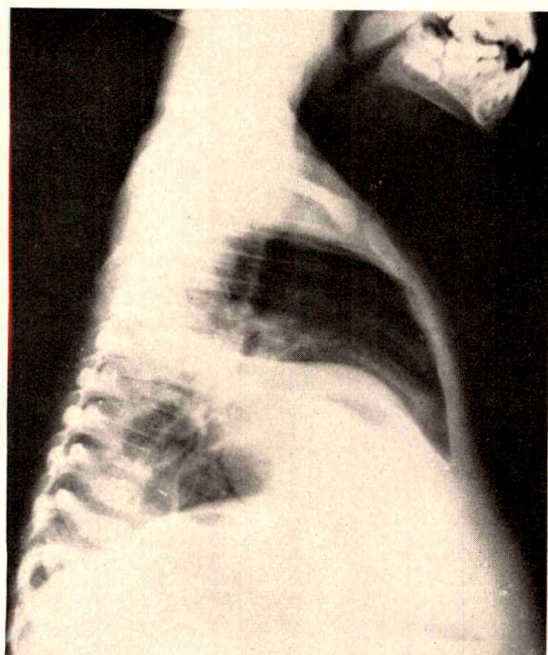


FIG. 5b.

FIG. 5—(a) Radiograph showing marked elevation of right dome of diaphragm; (b) after aspiration of 80 ml. of pus from liver; air can be seen in abscess cavity.

Dysentery or History of Dysentery. Twelve (23%) of the children had dysentery on admission and a past history of dysentery was obtained in a further 27 (51%). Thus 73% had antecedent or concomitant dysentery, which is similar to the findings in adults.

The absence of amoebae in the stools by no means excludes the diagnosis of amoebiasis, amoebae being found in only 13 (29%) of the 45 in whom stools were examined. Of seven who died before stool examination, three were found to have no bowel lesion at necropsy. In 13 necropsies in which amoebic ulceration of the bowel was found (eight of whom had extensive ulceration) amoebae were found before death in only two.

Nature of Pus. Classical 'anchovy-coloured' pus should not be anticipated as it was usually grey-green or grey-yellow at first aspiration and only at subsequent aspirations took on the pink or red-brown colour. Roach (1958) found that the abscess contents were yellow in over 90% of subjects at necropsy and concluded that 'only rarely at necropsy does the liver abscess contain the "anchovy-type" material considered by many to be characteristic'.

Opinions differ regarding the incidence of amoebae in the abscess contents. DeBailey and Ochsner (1951) found amoebae in 26% of 263 patients. In my series amoebae were found in the pus in eight (20%) of 40 cases aspirated and at necropsy in 13 (62%) of 21 cases. With recently improved technique, the Amoebiasis Research Unit, Durban, in a series of 71 consecutive liver abscesses in adults, have observed and/or isolated amoebae from 57 (80%) cases (Maddison, 1959). In future, therefore, we may find amoebae in aspiration specimens with greater frequency.

The pus was characteristically bacteriologically sterile in 36 (90%) of the 40 cases aspirated. In four bacteria were isolated from the first aspirate, but in no case did secondary infection occur as a result of aspiration.

Complications

Rupture of Abscess. This occurred in five patients (three fatal). In one, intrapulmonary rupture was followed by clinical improvement and recovery. In another, after two aspirations, rupture occurred through the abdominal wall. This infant made a remarkable recovery as he seemed moribund on admission. Two died shortly after admission from intraperitoneal rupture, and one case died suddenly following rupture of the abscess into the pericardium and pleural cavity.

Brain Abscess. This rare complication was found at necropsy in an infant aged 5 months who had a

massive abscess in the right hepatic lobe and multiple small abscesses in the left lobe. Amoebae were found in the brain abscess which had caused quite extensive cerebral softening.

Jaundice. Lamont and Pooler (1958) found jaundice in six of their 16 fatal cases. In my series it occurred in only one case, autopsy revealing two large abscesses producing mechanical obstruction to the biliary system (Fig. 6).



FIG. 6.—Necropsy photograph of liver from infant aged 4 months. Two large abscesses produced mechanical obstruction of biliary system with large mucocoele of gall bladder.

Mortality

There were 30 deaths, i.e. a mortality rate of 57%. Only two infants, aged 5 months and 7 months, recovered out of the 17 cases under 1 year of age.

The mortality rate in children cannot be assessed since no large series has been reported. In a study of 77 consecutive African patients with liver abscess Wilmot (1949) found a mortality rate of 11.7%. DeBailey and Ochsner (1951) reported an overall mortality of 22.2%, the mortality in their series being 100% in multiple abscesses but only 11% in those with single lesions. Multiple lesions undoubtedly worsen prognosis for they were present in 12 of the 21 children in whom autopsies were performed. Twelve cases were moribund and died soon after admission.

Treatment

Specific Anti-amoebic Therapy. Excluding the six cases where the correct diagnosis was not made, all received emetine. To those who survived long enough emetine was given for 10 days, the daily dose varying from gr. 1/8 to gr. 1/4, depending on the weight of the patient. Ten received a further seven-day course of emetine. Chloroquine diphosphate was used in an initial dose of 0.5 g., followed by 0.25 g. daily for 15 to 21 days. As chloroquine

therapy alone is followed by a significant relapse rate (Harinasuta, 1951; Wilmot, Powell and Adams, 1958), a combination of emetine and chloroquine may be the best form of treatment. In addition tetracycline or its derivatives and diiodo-hydroxy-quinoline were given when dysentery was present. Antibiotics are of no value in the treatment of liver abscess (Wilmot, Armstrong and Elsdon-Dew, 1952; Wilmot, Powell and Elsdon-Dew, 1958; Powell, Wilmot and Elsdon-Dew, 1959). Penicillin was usually employed while aspiration was being carried out as a precaution against secondary infection.

Supportive Measures. Intravenous fluids and blood transfusions were used when indicated. The maintenance of hydration and electrolyte balance is of paramount importance when serious dysentery is present.

Aspiration. This was done in 40 cases: 12 were aspirated once only, 18 on two to four occasions, and seven on five to seven occasions; three required 12, 13 and 17 aspirations respectively. From the latter case a total of 1,688 ml. of sterile pus was removed.

Surgical Drainage. One 5-month-old infant was treated by surgical drainage with good result. A further infant, after seven aspirations, developed a midline sinus and a residual small abscess was evacuated surgically. Rapid and complete cure followed. The last case in this series was immediately submitted for surgical drainage when bacteria were isolated from the first aspirate and cure followed.

Discussion

In African children in Durban amoebic liver abscess is commoner than elsewhere and for this reason an acute awareness of the condition in childhood is necessary. This condition should always be kept in mind in the differential diagnosis of hepatomegaly, especially tender hepatomegaly, even in the absence of dysentery or a history of antecedent dysentery. The difficulty in determining in a small crying infant whether hepatic tenderness exists is freely admitted. Another feature occasionally making diagnosis difficult is abdominal distension. However, exploratory transcostal needling would appear justified if amoebic liver abscess is suspected, as early diagnosis is one of the most important factors in lowering the attendant high mortality.

The clinical manifestations of amoebic liver abscess in children are similar to those in the adult, except that fever is a more frequent finding. Failure of response to therapy shown by a continuing high fever and increasing anaemia in children with

dysentery or a history thereof should suggest the possible presence of an hepatic complication. However, concomitant or antecedent dysentery can be expected in only about two-thirds of cases. With adequate treatment of amoebic dysentery there is usually improvement of the general condition of the child within about five days. Haematological changes, especially anaemia and leucocytosis, are of value in making a diagnosis. As in the adult, while radiological changes when present assist the diagnosis, their absence does not preclude it.

Most workers state that conservative treatment with amoebicidal drugs and closed drainage by repeated aspiration is best except where secondary infection is present. DeBakey and Ochsner (1951) showed a striking difference in mortality with conservative therapy consisting of emetine with or without aspiration compared with open operation. They advocate open drainage immediately if on first aspiration the abscess is secondarily infected.

Wilmot (1958) considers that the main indications for open drainage are:

(1) Failure to aspirate pus from patients with suspected liver abscess whose condition is not responding to emetine and/or chloroquine.

(2) Secondarily infected abscesses which do not respond to aspiration and local and systemic antibiotics.

(3) In some cases after rupture has occurred, in order to drain the pus from other loci.

(4) Cases not improving despite repeated aspiration and specific therapy.

In view of the high mortality rate, in retrospect it might have been advisable to undertake surgical drainage in those who required numerous aspirations. In future more thought should be given to those indications and selected cases should be submitted to surgery. Not all cases of amoebic liver abscess require aspiration on specific anti-amoebic treatment. During the period under discussion there were an additional 14 cases of undoubted amoebic liver abscess, but as confirmatory aspiration was not carried out these cases have been excluded from this series.

The management and treatment of amoebic liver abscess in children is basically the same as that advocated for adults.

Summary

Cases of amoebic liver abscess occurring in 53 African children are reported.

The importance of awareness of the condition and early diagnosis is stressed.

The condition can occur at any age, the youngest case in this series being 8 weeks.

There is not the distinct male predominance that is noted in the adult.

The abscesses are frequently multiple in children.

The important clinical features and difficulties in diagnosis in childhood are discussed.

The mortality is high (in this series about 57%) and only by early diagnosis may complications be prevented.

I wish to record my thanks to Dr. H. L. Wallace, Head of the Department of Paediatrics, University of Natal, to Dr. Pauline Klenerman, in whose wards these cases were treated, and to Dr. S. Disler, Medical Superintendent of King Edward VIII Hospital, Durban, for facilities. I am especially indebted to Dr. R. Elsdon-Dew, Dr. A. J. Wilmot, Dr. S. J. Powell and Dr. N. Lamont for much valuable criticism and advice. Finally, I wish to record my thanks to Miss A. Killerby for the photographs and to the staff of the Amoebiasis Research Unit for access to the literature.

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PERIPROSTATIC HAEMATOMA AND PROSTATIC ABSCESS IN THE NEONATAL PERIOD

BY

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The object of this contribution is to draw attention to a hitherto undescribed lesion, peri-prostatic haematoma, and to discuss its relationship to prostatic abscess occurring in the neonatal period. Both disorders have been wholly or partially responsible for a severe but remediable lower urinary tract obstruction in a series of infants observed at The Hospital for Sick Children, Great Ormond Street. The aetiology of the conditions, and even the exact pathological anatomy, remain obscure for, since all cases survived, only clinical data concerning them are available.

Prostatic abscess in an infant has been described on a number of occasions (Campbell, 1929; Szenkier, 1929; Fox, 1934; Alison and Le Tan Vinh, 1952; Boy, Wallon and Lauras, 1953). We have also treated a staphylococcal prostatic abscess in an infant, a case previously reported by George (1953), which is now summarized below.

Case 1. A previously healthy boy, aged 1 month, developed a hard red swelling on both sides of the scrotum; four days later he vomited after feeds and his abdomen was distended, due mainly to an enlarged bladder. Catheterization brought a marked but not complete improvement. The following day gross distension of the abdomen recurred and again catheterization released a clear urine. An abscess pointed in the right scrotum and was opened, releasing 7 ml. of thick sticky pus, which on culture grew *Staphylococcus aureus*. Subsequently catheterization was unsuccessful and the boy was transferred to The Hospital for Sick Children. His temperature had been only slightly raised and he was having small frequent green stools with much mucus. On admission the abdomen was distended and rather tympanitic and rectal examination revealed a small rectum compressed anteriorly by a cystic swelling, apparently in continuity with the bladder. The left epididymis was thickened; the right testicle and scrotum were hard with a discharging sinus inferiorly. Enlarged lymph nodes were present in both groins. The blood urea was normal and the urine sterile, but there was a leucocytosis (W.B.C. 21,200, 73% neutrophils). On the same day a suprapubic cystostomy was performed and a

tensely distended, thin-walled bladder was found. A fluctuant swelling was present beneath the trigone, elongating it and extending downwards behind the urethra. The bladder itself was normal. A perineal incision was made immediately in front of the rectum and a sinus forceps was guided into a large abscess cavity by a finger in the rectum. About 2 oz. of thick pus were evacuated. On culture there was a heavy growth of coagulase-positive staphylococci and a few colonies of *Escherichia coli*.

After three days there was a recurrence of the scrotal abscess and a certain amount of greenish-yellow pus was obtained, which on culture again grew *Staph. aureus*. Rectal examination showed some thickening in the prostatic region when the child was discharged on the fifteenth day. Two months later he was completely symptom-free.

There can be little doubt that the abscess in this case arose within the prostatic gland. It was a strictly midline swelling, closely resembling a prostatic tumour, and the simultaneous occurrence of epididymitis confirmed its prostatic origin. As in similar cases occurring in adult life, there must be some doubt as to whether the infection, which was clearly haematogenous, started in the prostate or in the epididymis, and the primary focus outside the genital tract was not identified. The presence of a staphylococcus suggests a skin sepsis, but none was found and the umbilicus was clean.

The cases which we place in the category of peri-prostatic haematoma (Cases 2 and 4, which are reported in full later) present several points of distinction. A mass was present in the pelvis which contained only old blood, sterile in Case 2, and infected with *Esch. coli* in Case 4 at a time when a blood culture also grew *Esch. coli*. The swelling as felt per rectum was lateral rather than median and was broadly based on the lateral pelvic wall, bulging into the cavity of the pelvis from one side only. It was thus distinguishable from a mass arising within the pelvic viscera. It appeared, therefore, that this effusion of blood had occurred in the fascial spaces

alongside the prostate and bladder a little in front of the rectum. No cause of the effusion could be identified, none of these cases had bleeding from any other source and there did not appear to be any coagulation defect. One infant had *Esch. coli* septicaemia in association with a urinary infection and in addition a urethral obstruction due to congenital valves. The possibility of a descending arteritis in the umbilical artery was considered as a source of the haemorrhage but there was no evidence of umbilical sepsis to support this hypothesis.

The clinical findings in Case 3 resembled those in Cases 2 and 4 but the swelling in the pelvis contained pus rather than blood: its lateral position suggested that suppuration might have occurred in a periprostatic haematoma but it could equally have arisen as a metastatic abscess in the prostate. In Case 5 the swelling resolved without surgical intervention; it is possible that an abscess cavity burst into the urethra in this child, suggesting a true prostatic lesion.

Retention of urine was the dominant clinical feature in all these infants. It was abrupt in onset and, although occurring within the first month of life, in only one was there any suggestion of a congenital abnormality. The bladder was tensely distended, the kidneys palpable and the blood urea raised. The urinary obstruction was due to pressure on the urethra and bladder neck: it was relieved as soon as the abscess or haematoma was evacuated. Urinary infection was present at some time in all instances, but probably resulted from catheterization. In Case 4 *Esch. coli* was already present before instrumentation and a septicaemia with severe collapse and dehydration at first concealed the real nature of the condition.

Drainage was obtained through a perineal incision: this method entails least disturbance of other organs but the track is apt to be long and narrow. It was found that refilling of the cavity could be minimized by stripping down the area with a finger in the rectum, and the fourth case settled down within a few days on this routine. Convalescence in all cases has been prolonged and the urinary infection has been difficult to eliminate. Some permanent damage to the upper urinary tract must be anticipated although the blood urea in all cases returned to normal.

Case Reports

Case 2. This boy, a first child, was born at full term on June 18, 1955 in a normal delivery and weighed 8 lb. 12 oz. The mother's pregnancy and puerperal period were uneventful apart from moderate anaemia. He was breast fed for one week, and then thrived on

bottle feeding (N.D. milk) having no complaints until 4 weeks old when, on July 13, he started vomiting after feeds and having diarrhoea with loose greenish stools without mucus or blood. The parents also noticed that the child cried after passing urine, although he had a good stream with no dribbling. On account of worsening of his symptoms, he was admitted to Thurrock Hospital on July 15 and was found to have abdominal distension and a full bladder; catheterization produced 13 oz. of pale clear urine. When catheterized again that evening another 14 oz. were obtained. On July 16 the bladder was again distended up to the umbilicus and the infant's general condition was poor. Catheterization was then unsuccessful: a suprapubic lumbar puncture needle was inserted and 9 oz. of urine were removed.

The child was transferred to The Hospital for Sick Children and on admission on July 16 he did not look well but cried fairly lustily. His colour was fair but he was moderately dehydrated, weighing 9 lb. 4½ oz. There was moderate tachypnoea and a suggestion of meningism but no pyrexia. The abdomen was distended with subcutaneous veins rather more obvious than usual. The bladder was up to the umbilicus but the kidneys could not be felt. Rectal examination revealed a large anterior mass bulging into the rectum. The provisional diagnosis was congenital urethral obstruction. Investigations showed:

(16.7.55) blood urea 134 mg./100 ml.; serum electrolytes: Cl 713 mg./100 ml. (121 mEq./l.), Na 345 mg./100 ml. (150 mEq./l.), K 21 mg./100 ml. (5.4 mEq./l.), CO₂ 21.2 vol. % (9.5 mEq./l.); Hb 86% or 12.73 g./100 ml.

(17.7.55) blood urea 142 mg./100 ml.; urine pale, turbid; S.G. 1016; protein 160 mg.%; deposit: masses of W.B.C.s in uncentrifuged urine; heavy growth of *Proteus* on culture.

(18.7.55) bleeding time 4 min. 55 sec.; clotting time 1 min. 40 sec.

Dehydration was corrected with intravenous fluids and bilateral pyelostomy was performed for drainage. The following day there was still a palpable cystic mass in the prostatic region and an operation was performed under a general anaesthetic. After catheterization, which obtained 5 oz. of urine, an exploratory needle was introduced through the perineum and entered a cystic cavity from which some dark blood was withdrawn. A small perineal incision was then made and through it 1 oz. of similar material was obtained. This cyst appeared to have no connexion with either the rectum or the lower urinary tract. A rubber drainage tube was left in place in the wound and the urethral catheter was left to drain the bladder. The contents of the cavity showed numerous R.B.C.s; an occasional polymorph but no organisms were seen. On culture there was no growth.

During the following days his general condition improved steadily and his blood urea fell. The left nephrostomy tube was removed on July 18, the right nephrostomy tube on July 22 and the urethral catheter on July 23. At that time the urine was sterile. As there seemed to be inadequate drainage and he was not able to empty his bladder completely, the wound was re-explored on July 26 and another drainage tube was

inserted. A sinogram was performed and outlined the cavity which was unconnected with any of the pelvic organs (Fig. 1). A wound swab showed on culture a light growth of coagulase-positive staphylococci and *Esch. coli*. In the following days the discharge became frankly purulent but diminished progressively in amount, and the pelvic mass gradually subsided. On September 4 he developed gastro-enteritis and he required several intravenous infusions and antibiotic treatment before he finally settled down. When he was discharged on October 2 he was having no difficulty with micturition, and the pelvic mass had practically disappeared, leaving only a rather general induration which extended across both sides of the pelvis.

When re-investigated three and a half years later, the urinary tract was normal on intravenous pyelography and cystoscopy, although he was still enuretic.

Case 3. A premature first-born male child was born on September 17, 1957, by normal delivery. He weighed 4 lb. 14 oz. and looked normal. He thrived on bottle feeding (N.D. milk) and had no complaints until 5 weeks old when, on October 23, he ceased to pass urine. His legs and lower abdomen were moderately oedematous and he vomited after all feeds. On the same day he was admitted to the Whittington Hospital where he was found to have a distended bladder.

He was transferred to The Hospital for Sick Children on October 24, when he looked ill and rather pale and greyish in colour but hydration was fair. He weighed 7 lb. 5½ oz. There was moderate oedema in the legs and lower abdomen, which was rather distended and tym-

panitic; the bladder was felt up to the level of the umbilicus. Both kidneys were easily felt, particularly the right, but did not seem to be enlarged. The penis, testicles and scrotum looked normal. Catheterization withdrew 4 oz. of dirty urine and rectal examination revealed an apparently painless, smooth and rounded mass in the pelvis, which prevented full introduction of the examining finger. The mass was situated rather lower down than would be expected for the bladder, although there seemed to be continuity of the two structures, the bladder wall being thickened and hard. The child's temperature was 96.4° F., but had risen to 101.4° F. next morning. The diagnosis of peri-prostatic abscess was made.

Laboratory investigations gave the following results: (25.10.57.) blood urea 79 mg./100 ml.; serum electrolytes: Cl 1578 mg./100 ml. (99 mEq./l.), Na 310 mg./100 ml. (134 mEq./l.), K 20 mg./100 ml. (5.1 mEq./l.); CO₂ 64.7 vol. % (29.2 mEq./l.); Hb 79% or 11.60 g./100 ml.; W.B.C. 29,500; neutrophils 65%; P.C.V. 40%; urine slightly alkaline; protein 80 mg.%; deposits nil; culture (catheter specimen) no growth.

At operation a needle was introduced through the perineum in front of the rectum; it entered the cavity of a peri-prostatic abscess and 20 ml. of thick greenish pus were removed with a syringe. Afterwards the opening was enlarged with a sinus forceps and a corrugated rubber drain was left in place. The pus showed a very large number of polymorphs and gram-positive cocci, which on culture produced a heavy growth of coagulase-positive staphylococci.

Following the operation micturition was normal. The

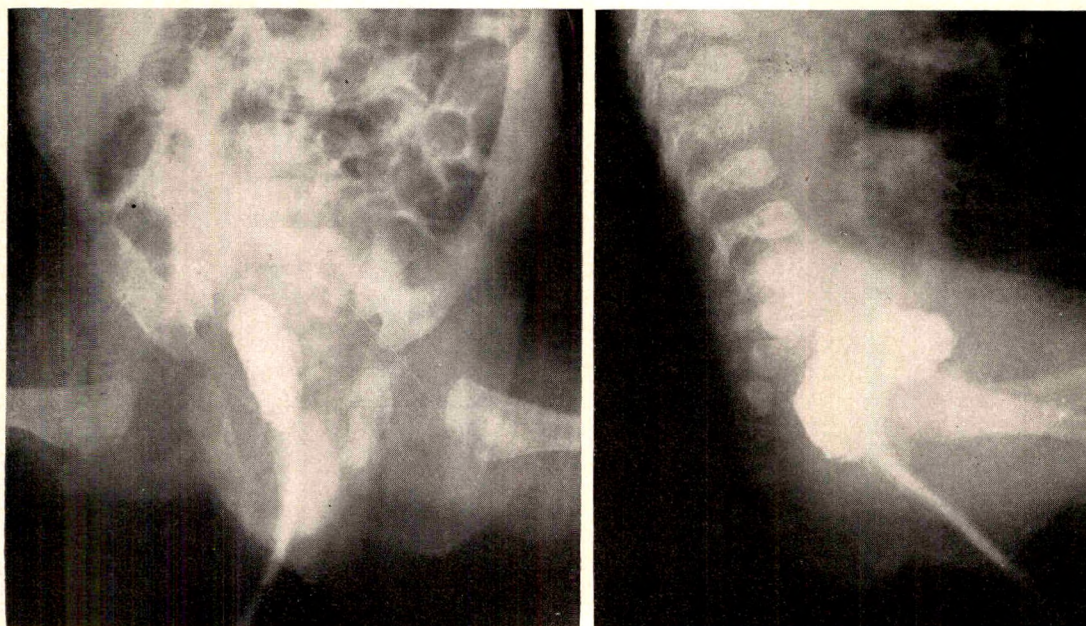


FIG. 1.—Case 2. Sinograms outlining haematoma cavity.

sinus had to be opened with forceps on two separate occasions, but he then had an uneventful convalescence and was discharged on November 9. The perineal wound was healed, he was taking feeds well, gaining weight, and had a good stream of urine. Rectal examination was normal apart from slight induration of the prostatic region.

Eighteen months later his adoptive parents wrote to say that he was in excellent health, and as they were living a long way from London they were not prepared to bring him up for examination.

Case 4. A third child was born at full term on May 21, 1958, in a normal delivery. The mother's pregnancy and puerperal period were uneventful. He weighed 8 lb. 12 oz. at birth.

During the first week his stools were rather frequent, small in amount and brownish in colour, and he lost weight steadily, looking rather lethargic. On June 2 he vomited once before and once after a feed. The vomit was at times projectile, containing some brown material but no definite macroscopical evidence of blood. He was sent to The Hospital for Sick Children with a diagnosis of pyloric stenosis.

On admission under Dr. Wilfrid Sheldon on June 3 he looked rather sallow but his hydration was fair, his weight being 7 lb. 13 oz. The abdomen showed no visible peristalsis and no pyloric tumour was felt. The liver was two fingers below the costal margin with a slightly irregular edge. The kidneys were enlarged and lobulated and the blood urea was 208 mg.%. A routine urine analysis showed infection with *Esch. coli*, and a blood culture performed the same day also showed a heavy growth of *Esch. coli*. Next morning the spleen was palpable and the child was put on Achromycin.

Two days later there was some generalized oedema, the kidneys were still enlarged and a distended bladder was also palpated. The blood urea was still raised and bilateral pyelostomies were performed for drainage. At operation the kidneys were found to be large but looked healthy and the pelves were not unduly distended. On the following day an examination under anaesthesia revealed a smooth round prostatic swelling. A needle was introduced through the perineum and altered blood was aspirated. An incision was made and a large amount of blood evacuated. A corrugated rubber drain was left in the wound and an indwelling catheter was used for bladder drainage. The blood produced on culture a heavy growth of *Esch. coli*.

In the afternoon following operation the child was still pale and lethargic and he was given a small blood transfusion. Next day the prostatic swelling had lessened and some more blood clots were expressed with the help of a rectal finger. The nephrostomy tubes were then removed. He was kept on intravenous fluids until June 10, and by that time his general condition had considerably improved. On June 11, although the kidneys were still palpable and the bladder distended at times, he was able to pass urine with a fair stream.

Subsequently he made only slow progress, interrupted by repeated urinary infections. By July 7 the blood

urea had fallen to 41 mg./100 ml., but micturition was not satisfactory. An intravenous pyelogram then showed considerable bilateral dilatation of the ureters and later an expression cystogram revealed the presence of typical congenital posterior urethral valves. This obstruction was treated endoscopically and normal micturition was restored but persistent urinary infection remained a troublesome feature and in November the excessively tortuous left ureter was shortened and straightened. Following that operation progress was more satisfactory, though there was still a slight pyuria.

In this case, therefore, the effusion of blood only exacerbated a pre-existing congenital obstruction.

Case 5. A first child was born at full term on May 5, 1953, in a normal delivery. The mother's pregnancy and puerperal period were uneventful. He weighed 6 lb. 13 oz. at birth and thrived on breast feeding supplemented by a bottle. He had no complaints until 2 weeks old when he was noticed to have a slight whitish discharge from beneath the prepuce and seemed to have pain on micturition, straining and screaming during the act. The urine looked cloudy, thick and whitish and the stream was reduced to a continuous dribble. On account of worsening of these symptoms, he was admitted on May 29 to Amersham General Hospital under Dr. Dermot MacCarthy, and the mucoid penile discharge was found to contain numerous pus cells. The abdomen was not distended but the bladder was full. On rectal examination there was a tense elastic swelling bulging anteriorly into the rectum, encountered immediately by the palpating finger. Following admission he passed increasing amounts of urine, with pus present macroscopically. A urine specimen showed very numerous pus cells and on culture grew *Staphylococcus pyogenes*. He received penicillin 100,000 units twice daily. On May 30, after passing about 1 oz. of pink pus, his urine became quite clear and pain on micturition almost disappeared. His temperature was never above 99.6° F., and throughout he took his feeds well, never vomiting. At this stage he was transferred to The Hospital for Sick Children. On admission he looked a normal healthy boy with good colour and hydration and weighed 7 lb. 12 oz. No umbilical infection or septic spots were noticed, the bladder was not distended, and the foreskin and urethral meatus were normal, no discharge being seen. Rectal examination showed a normal anus and rectum and a soft but enlarged prostate (more on the right side than on the left). No other relevant findings were detected on clinical examination. Within a week the prostatic swelling completely subsided, leaving only a slight induration. Bowel actions were normal, appetite was good, temperature was normal and the child was gaining weight. Micturition was normal with a good stream of clear urine when the child was discharged on June 6.

Investigations showed: (31.5.53.) blood urea 23 mg./100 ml.; Hb 102% or 14.3 g./100 ml.; R.B.C. 4,290,000; W.B.C. 23,200; neutrophils 53%; urine neutral, no protein; heavy growth of *Esch. coli* and moderate growth of coagulase-negative staphylococci on culture.

Summary

Prostatic abscess and peri-prostatic haematoma are both lesions which cause a severe lower urinary tract obstruction in young infants: they are not necessarily associated with a congenital abnormality and the prognosis is good if the cavity is adequately drained. The abscess is probably metastatic in origin or may follow suppuration in a haematoma, but no satisfactory explanation of the haematoma formation is advanced.

The diagnosis is easily made by rectal palpation after the bladder has been emptied by catheter. A strictly prostatic abscess may be difficult to distinguish from a tumour by palpation but an exploratory needle puncture will settle the issue. The peri-prostatic haematoma is based on the lateral

pelvic wall and does not resemble a visceral swelling.

Urinary retention is relieved by drainage of the abscess or haematoma cavity and neither a urethral catheter nor cystostomy is required as long as the cavity is kept empty. Perineal drainage is satisfactory if combined with daily 'stripping' from the rectum. Chemotherapy is required as an adjunct.

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GENERALIZED BRONCHIECTASIS ASSOCIATED WITH DEFICIENCY OF CARTILAGE IN THE BRONCHIAL TREE

BY

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Bronchiectasis may occasionally affect almost the entire bronchial tree. Such changes can be the result either of developmental defects of the bronchial tree or of acquired inflammatory disease. For example, cystic lung and cystic bronchiectasis can result from both causes.

The purpose of the present paper is to record five patients with a most unusual type of generalized bronchiectasis, and to submit evidence that its basis is deficiency of the cartilage of the bronchial walls, probably developmental in origin.

Material and Methods

The five patients have been studied clinically for periods between three and nine years. Radiological, bronchoscopic, bronchographic and bacteriological examinations have been carried out at suitable intervals. The lungs of one of the two patients who died were examined in the fresh state and then fixed by injecting the bronchi with formalin. Studies consisted of macroscopic dissection of several segmental bronchi and their divisions, and serial histological sections of four lung segments (apical, anterior and posterior basic and lingula of the left lung). The stains used were haematoxylin and eosin, Verhoeff van Gieson and periodic acid stain of Schiff. The bronchi were identified numerically by counting distally from the segmental bronchus (Hayward and Reid, 1952); see Appendix.

Clinical Features

Case 1. J.G. In October, 1949, a boy aged 2½ years was referred to the Royal Children's Hospital with a cough, irregular fever and wheezy breathing, which

developed following an attack of morbilli six weeks previously. Before this he was well and had no serious illnesses. His doctor had made a diagnosis of unresolved pneumonia and asthma, and had unsuccessfully treated him with antibiotics and antispasmodics. He was found to be thin, with slightly cyanosed lips, and his breathing was difficult and audibly wheezy. His chest was barrel-shaped, and inspiratory and expiratory rhonchi and fine crepitations were heard over the entire chest. A radiograph of the chest showed prominent hilar shadows and bronchovascular markings, some haziness in the right middle lobe and lingula and slight pulmonary emphysema. His Mantoux test 1:1000 OT was negative and *Streptococcus viridans* was grown from a small blob of expectorated mucus. Bronchoscopic examination was normal apart from some muco-purulent secretion in both bronchi. A remarkable bronchographic picture was seen on the x-ray screen, the whole bronchial tree from the first division of the segmental bronchus to the fifth or eighth division (depending on the size of the segment) expanded and narrowed with inspiration and expiration (Fig. 1a and b), while the fourth to sixth or eighth divisions of the right bronchial tree were like a series of elongated balloons which were being inflated and deflated (Fig. 2a and b). These changes were more pronounced in the right than in the left lung. At the site of bronchial branching the movement was not so marked. Apart from one or two small areas, no oil entered the fine divisions of the bronchial tree, even though dye was still present in the bronchial tree 40 hours later (Fig. 3a and b).

Treatment with penicillin and sulphonamides and postural coughing led to slight improvement in his general condition but the cough and wheeze persisted and he periodically had attacks of fever and malaise. As he grew older his symptoms lessened and his general health improved. Nine years after the onset he is in fair health but is unable to run without becoming very short-winded, has a constant slight inspiratory and expiratory wheeze and cough. His chest is barrel-shaped with a pigeon deformity and Harrison's sulcus.

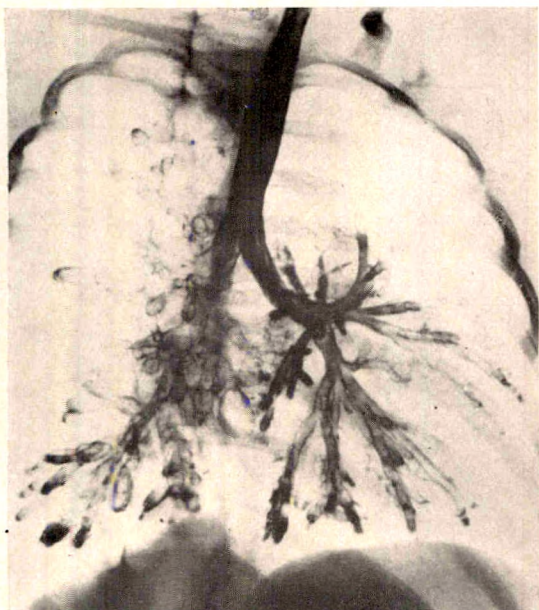


FIG. 1a.—Case 1. J.G. Bronchogram in inspiration showing 'cystic' dilatation of right bronchial tree and cylindrical dilatation of left.

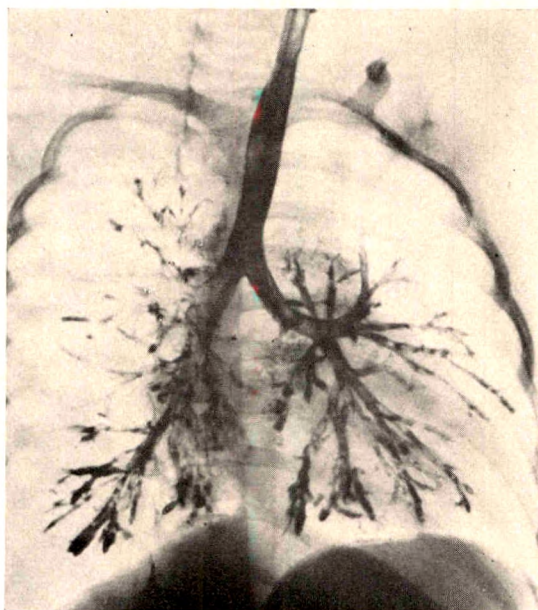


FIG. 1b.—Case 1. J.G. Bronchogram in expiration, showing collapse of bronchi.

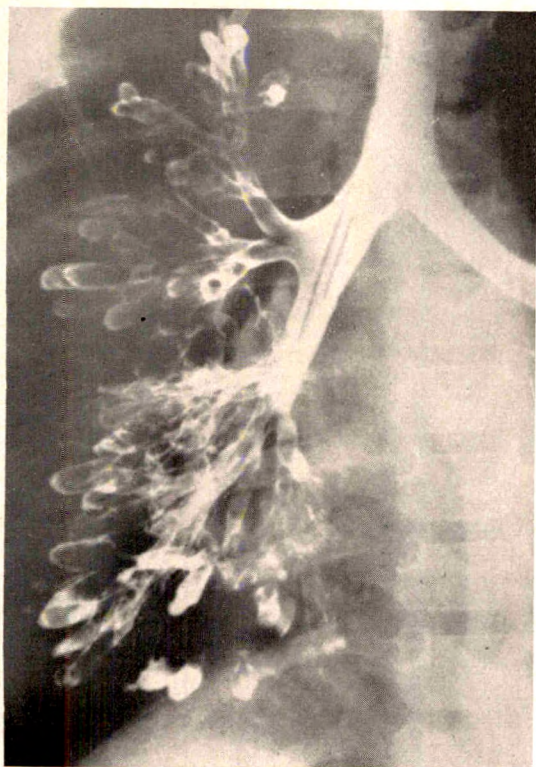


FIG. 2a.—Case 1. J.G. Bronchogram of right bronchial tree in inspiration showing gross bronchial dilatation beyond segmental bronchi but no bronchiolar filling.

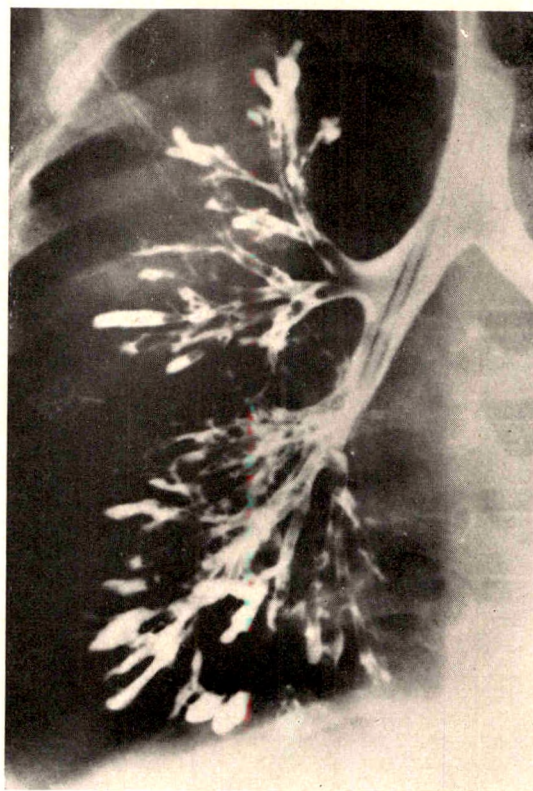


FIG. 2b.—Case 1. J.G. Bronchogram of right bronchial tree in expiration showing collapse of bronchi.

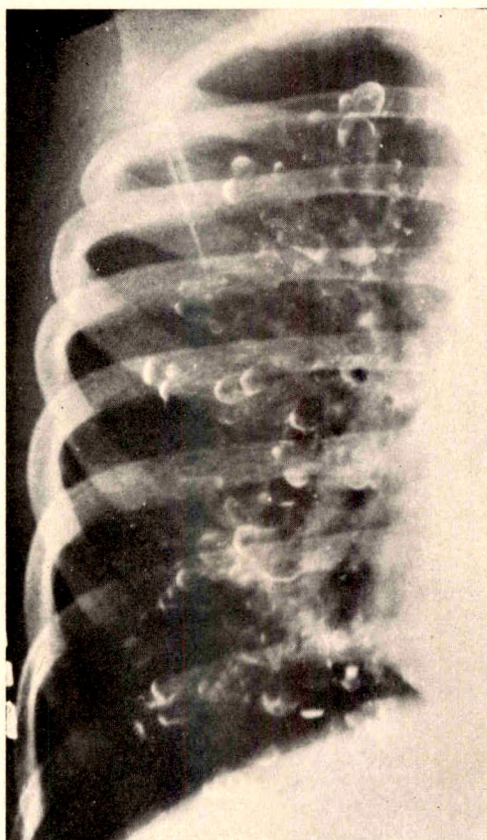


FIG. 3a.—Case 1. J.G. Film in inspiration taken 40 hours after Fig. 2a showing retention of dye and no filling of small bronchi.

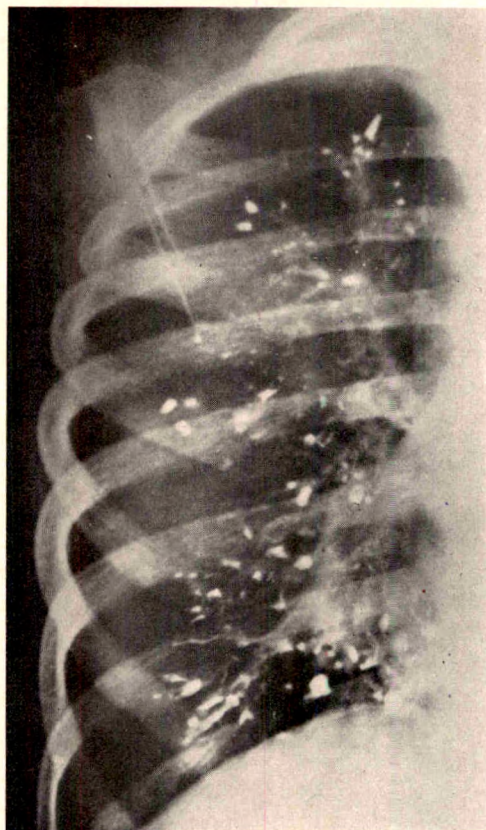


FIG. 3b.—Case 1. J.G. Film in expiration taken 40 hours after Fig. 2a showing collapse of bronchi.

Case 2. D.S., the first baby of healthy parents, made normal progress until the age of 10 months when he developed a running nose, cough and wheezy breathing. A diagnosis of asthmatic bronchitis was made, but treatment with antibiotics and antispasmodics failed to relieve his symptoms. The cough, wheezing and febrile attacks gradually became worse and his general health deteriorated.

At the age of 2 years 8 months when he was admitted to the Royal Children's Hospital in July 1952 he was ill with distressed wheezy breathing and slight cyanosis of lips and ears. He had a barrel-shaped chest with bilateral Harrison's sulcus, the air entry over the entire chest was poor, and inspiratory and expiratory rhonchi and numerous fine crepitations were heard over the whole lungs. The heart was displaced to the left and the percussion note over the left upper lobe was impaired. The abdomen was distended, the fingers clubbed and he expectorated some mucopus, culture of which grew *Staphylococcus aureus*. A chest radiograph showed collapse of the left upper lobe and mediastinal shift to the left, and the peripheral lung field of the right lung and the left lower lobe

appeared emphysematous. Bronchoscopy was normal apart from a small amount of mucopus in both bronchi. Bronchographic examination was almost identical with that in Case 1, but the bronchiectatic changes were most pronounced on the left side where the left lung was collapsed. Expansion and partial collapse were observed from the first division of the segmental bronchus to the fifth or eighth division, according to the segment, but no dye entered the bronchiolar tree.

Treatment with antibiotics, antispasmodics and postural coughing afforded only slight relief. His condition gradually deteriorated and he died of respiratory failure at the age of 3 years 2 months. Autopsy was refused.

Case 3. J.C. was a healthy baby of healthy parents until she developed pink disease at the age of 14 months. She was left with a slight cough and occasionally had a slight wheeze. At the age of 2 years 3 months she developed measles following which her cough became worse, her breathing difficult and wheezy, her stools pale and offensive and her body wasted. A diagnosis of

fibrocystic disease of the pancreas was made. Following treatment with chemotherapy she very slowly improved.

When seen at the Royal Children's Hospital in May 1953 at the age of 4 years she appeared in fair general health, had a rather barrel-shaped chest, a slight wheeze and produced a little mucopus on posture. Impaired percussion note and tubular breathing were heard over the left lower lobe and scattered crepitations over the entire chest. A radiograph of the chest showed increase in the broncho-vascular markings, collapse of the left lower lobe and somewhat emphysematous peripheral lung fields. Duodenal enzymes and fat balance were normal. Bronchoscopy was normal apart from a little mucopus in the left lower lobe bronchus. The bronchogram showed changes similar to those in Cases 1 and 2 with the exception that in the right lower lobe and pectoral segment of the left upper lobe the bronchial calibre changes during respiration were not so pronounced and there was filling of some of the smaller bronchi and the bronchiolar tree.

From the age of 4 years up to 9½ years she slowly and steadily improved in general health. She has a very slight cough at present and usually no sputum and only wheezes and coughs sputum if she develops a cold or has a feverish attack. These attacks used to occur every few months but now she has them only occasionally. She can run but gets short of wind easily. A ventilatory capacity test at the age of 9 years showed figures indicative of a moderately severe obstructive type of ventilatory defect.

Case 4. A.D., a healthy baby of healthy parents, made normal progress until the age of 10 months when she contracted morbilli. After this she developed a cough, rapid wheezy breathing and would not eat. As these symptoms persisted she was referred to the Royal Children's Hospital in November 1955 aged 1 year with a diagnosis of unresolved broncho-pneumonia. She was moderately well nourished, had slightly rapid laboured respirations with an audible inspiratory and expiratory wheeze. Numerous inspiratory and expiratory rhonchi and fine crepitations were heard all over the chest. A radiograph showed prominent bronchovascular markings and some emphysema in the peripheral lung fields. Culture of a cough swab yielded *Staph. aureus* and *Proteus*. Treatment with one of the tetracycline group of drugs resulted in some general improvement but the cough and wheeze persisted, she continued to run episodes of fever and her signs remained unchanged. Bronchoscopy at the age of 2 years was normal apart from some mucopus in both bronchi. A bronchogram showed symmetrical expansion and collapse of the bronchial tree from the region of the first segmental divisions down to the fifth or eighth branching, according to the segment. Apart from a few areas the dye did not enter small bronchi or bronchioles.

During the two years follow-up her general health has slowly improved. She still has a slight cough and an audible inspiratory and expiratory wheeze, but during the last year has only had two mild feverish attacks. Her chest is deformed with a marked pigeon chest, bilateral

Harrison's sulcus and she breathes with the upper part. She becomes short-winded if she attempts to run.

Case 5. A.W., a premature baby weighing 4 lb. 7 oz., developed a cough and wheeze at the age of 2½ months. The cough and wheeze persisted, he ran frequent febrile episodes and was said to be cyanosed at times. When first seen at the Royal Children's Hospital in December 1952 at the age of 2½ years he was a thin, poorly nourished child (weight 20 lb.) with slightly cyanosed lips and ears. His breathing was difficult and there was a moderately loud inspiratory and expiratory wheeze. The chest was barrel-shaped, movement being predominantly in the upper portion, and numerous fine crepitations and rhonchi were heard all over the chest. No other abnormalities were found. A radiograph of the chest showed increased bronchovascular markings and very few vascular markings in the peripheral lung fields. His Mantoux test 1:1000 OT was negative, his stools did not show any fat globules and culture of a cough swab yielded *Staph. aureus*. Bronchoscopic examination was normal apart from some reddening of the bronchial mucosa and a small amount of purulent exudate in both bronchi. The bronchogram showed that the segmental bronchi down to the fifth or eighth divisions, according to the segment, dilated and narrowed with inspiration and expiration (Fig. 4a and b), but not to the same degree as in the first three patients. Several areas in both lungs showed some bronchiolar filling. Dye was still present in the dilated bronchi 48 hours after instillation.

During the next two years until his death at the age of 4 years 8 months he had a constant cough, increasingly difficult breathing with cyanosis and frequent episodes of fever. Gradually he developed pulmonary hypertension, his heart enlarged, and an angiogram showed some dilatation of the right auricle, right ventricle and pulmonary artery, while the pulmonary tree showed irregular tortuous small arterioles with delayed passage of dye. Cardiac catheterization showed moderate pulmonary hypertension.

Morbid Anatomical Features of Case 5

Pathological changes were confined to the respiratory and cardiovascular systems. In the fresh state the lungs appeared congested and felt nodular. Bronchi distal to the main segmental divisions were dilated and the mucosa of all bronchi was oedematous and inflamed. The pulmonary arteries were dilated and slightly atheromatous, and the heart showed moderate hypertrophy and dilatation of the right ventricle. After formalin fixation further macroscopic and microscopic studies were carried out.

Macroscopic Appearances. The segmental bronchi were normal, but the second and third divisions were dilated, being of similar calibre to the segmental bronchus. Many of the dilated lateral divisions suddenly tapered to a fine thread barely possessing

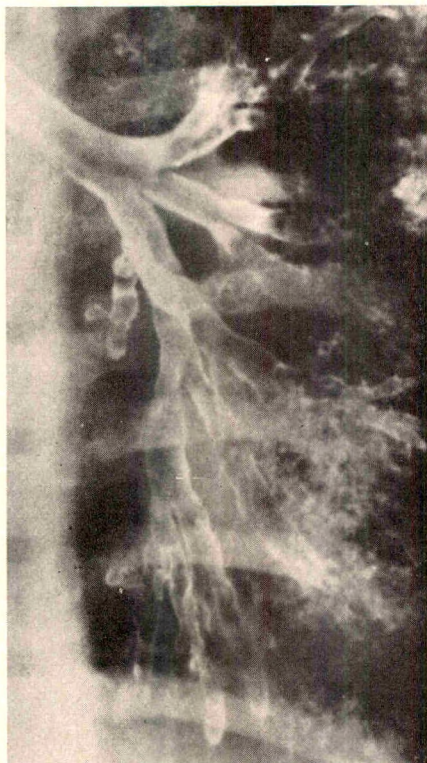


FIG. 4a.—Case 5. A.W. Bronchogram showing bronchial dilatation in left lower lobe. Film in inspiration.

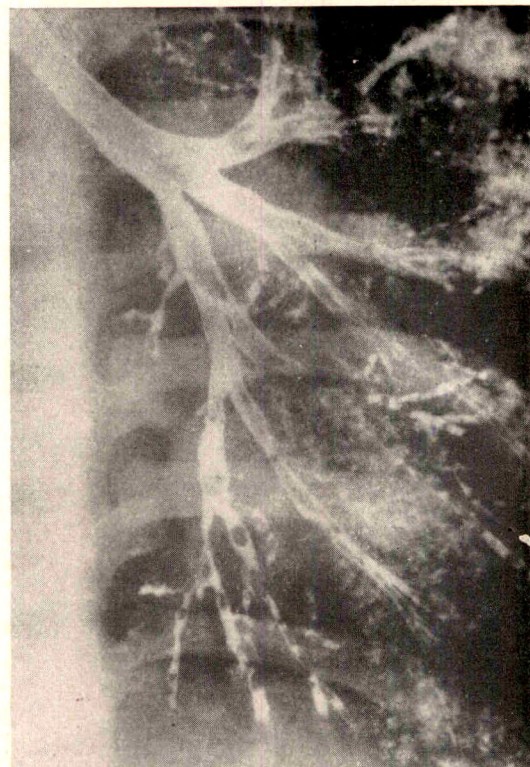


FIG. 4b.—Case 5. A.W. Bronchogram showing collapse of bronchi in left lower lobe. Film in expiration.

a lumen. Divisions of the axial bronchi distal to the third division gradually tapered, but were still greatly dilated compared with the normal controls (Fig. 5a and b). The most striking feature was the extreme softness of the bronchial walls, which, despite formalin fixation, were as flabby as blood vessels. In nearly all of the bronchi dissected the transition from firm rigid walls to soft easily compressible structures was sudden and occurred along the course of the second or third division. From this point to the periphery the walls remained soft, except where division occurred when a slight resistance could be felt in the acute angle of the bifurcation. In several dissections it was



FIG. 5a.—Case 5. A.W. Dissection showing dilated bronchi, partly unroofed, of lingula and pectoral segments. (Slightly reduced.)



FIG. 5b.—Dissection of normal anterior basic bronchus and its divisions. (Slightly reduced.)

difficult to trace an axial bronchus to the periphery, bronchial branching being dichotomous and forming two divisions of identical calibre. In many instances, however, a true axial bronchus was present (see Appendix).

Microscopical Findings. These were as follows.

SEGMENTAL BRONCHI (FIRST DIVISION BRONCHI). The mucosa showed pseudostratified ciliated columnar epithelium with areas of squamous metaplasia (mucosa less folded than normal) resting on a narrow condensed band of collagen 7-20 μ in thickness. Foci of lymphocytes were present with little apparent relation to the nature or state of the

mucosal cells (*viz.*, pseudostratified, ciliated or non-ciliated, squamous metaplasia).

Muscle coat was present in all bronchi examined. It was very thin in places (30-40 μ) but elsewhere was quite thick (200-300 μ). It was often thin next to cartilage plaques and thicker where cartilage was absent. Beneath the muscle and merging with it was a network of collagen and elastic fibres, thicker and more prominent in areas deficient in cartilage.

Individual plaques of cartilage varied in size and appeared 'chunky', i.e. they were not long and thin as in the normal; in cross-section their size varied from 700 μ to 2,500 μ and, as in the normal, their edges merged with the surrounding fibro-elastic network.

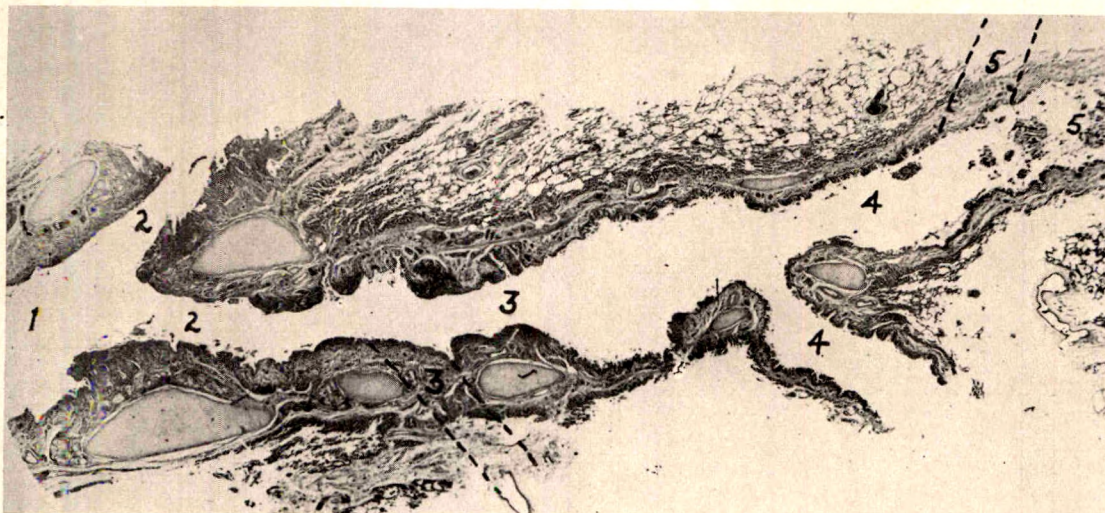


FIG. 6a—Case 5. A.W. Longitudinal section of segmental bronchus showing cartilage distribution. (Note two bronchi arose out of plane of section. Bronchial divisions are numbered.)

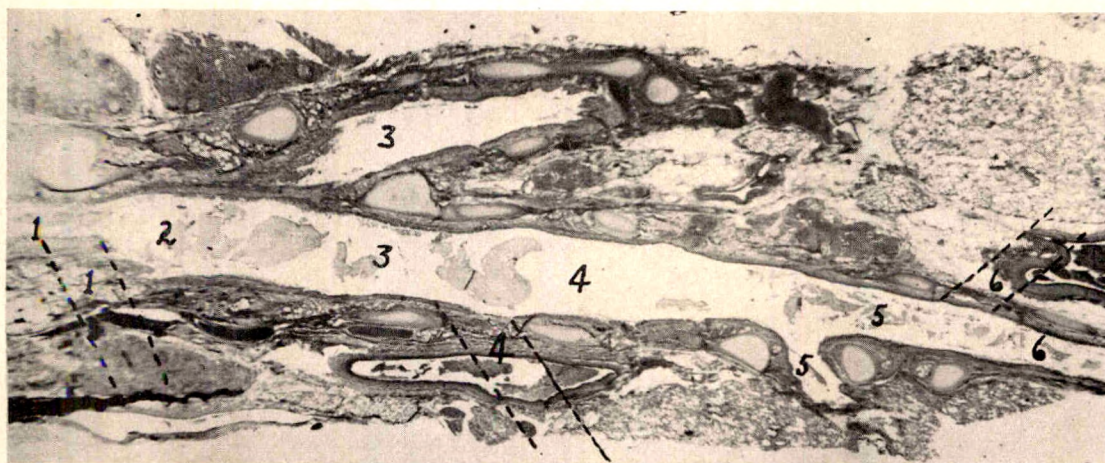


FIG. 6b—Longitudinal section of segmental bronchus showing cartilage distribution in the normal. Bronchial divisions are numbered. Three bronchi arose out of plane of section.

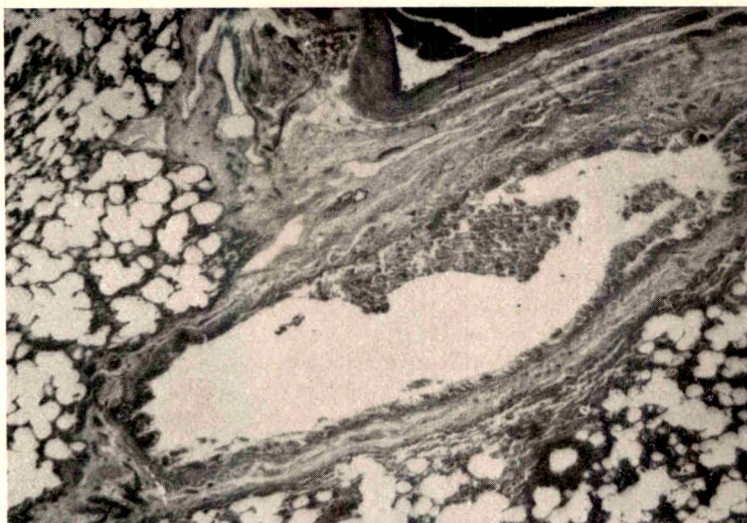


FIG. 7a.—Case 5. A.W. Showing a cross-section of a fifth division axial bronchus. Note complete absence of cartilage in wall. ($\times 25$.)



FIG. 7b.—Normal control, showing cross-section of fifth division axial bronchus. Note cartilage present. ($\times 25$.)

SUB-SEGMENTAL BRONCHI (SECOND AND DISTAL DIVISIONS). More numerous areas of squamous metaplasia were present in the mucosa, otherwise the pattern was similar to that in the segmental bronchus.

Muscle was invariably present, sometimes thin (30-40 μ) but quite often normal in appearance and thickness. Isolated areas of small round cell infiltration were present, some of which were associated with partial fibrous replacement of muscle.

bronchioles and moderately severe. Vascular thickening was slight, involving the medium-sized and small arterioles.

Discussion

The clinical features in all five children were very similar. The disease commenced in infancy, either insidiously as mild bronchitis or more acutely with morbilli. Persistent cough, wheezy difficult breathing, recurrent febrile episodes and widespread

One must distinguish between the axial bronchus and its lateral divisions, all lateral divisions being devoid of cartilage whereas in occasional cases the third and even fourth division axial bronchi contained isolated cartilage plates. Thus, examination of sections from the anterior basic bronchus (left lung) showed cartilage distribution as follows. The segmental bronchus and the first, second and third division bronchi contained cartilage. In the third division bronchi, the plaques were widely separated and were small. In the fourth division bronchus, very occasional plaques only were visible. Examination of the lingula bronchus showed cartilage as far down as the third division but it was absent distal to this. All other bronchi from the end of the second division showed walls devoid of cartilage except at each point of bifurcation where a small nub of cartilage was present in all cases down as far as the fifth, sixth and seventh division bronchi (Figs. 6a and b; 7a and b).

The following changes were found in the more peripheral parts of the lungs. Bronchiolar obliteration was often severe and extensive (Fig. 8). Bronchioles were far less numerous than in the normal controls. Some that had been recently obliterated were still recognizable, but many were represented only by small areas of scarring. Emphysema was focal, related to obliterated

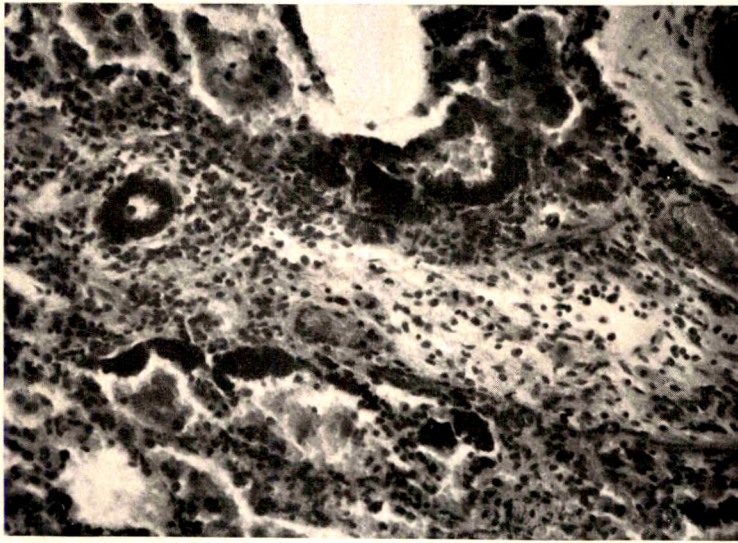


FIG. 8.—Case 5. A.W. Showing bronchiolar obliteration. ($\times 125$.)

inspiratory and expiratory rhonchi and crepitations were the main clinical features. The chest was deformed as a result of diffuse bronchial and bronchiolar obstruction and pulmonary emphysema. As the clinical pattern and physical signs were those of chronic or subacute bronchiolitis with recurrent exacerbations, it was no wonder that a diagnosis of asthmatic bronchitis, or non-specific bronchiolitis, or fibrocystic disease of the pancreas was made.

The course of the disease varied considerably. In two patients it was steadily downhill, death occurring at the ages of $4\frac{3}{4}$ and 3 years. Both patients died of progressive respiratory failure, the result of chronic infective bronchiolitis and pulmonary hypertension. One of the three living children is in good health, the only symptoms being a little cough and breathlessness out of proportion to the degree of physical activity. The other two are severely limited, any active exertion resulting in breathlessness. As these children have grown older, infection has become less and their general health correspondingly improved.

The clinical features and bronchographic appearances of Case 1 suggested that expansion and narrowing of the bronchial walls with respiration was due to considerable structural weakness. Lack of cartilage seemed to be the probable structural weakness as similar expansion and collapse of the walls of the trachea and main bronchi had been observed when cartilage was absent from mal-development (Ferguson and Neuhauser, 1944; Evans, 1949; and Holinger and Johnston, 1957).

The gross morbid anatomical findings in Case 5 revealed dilatation of the sub-segmental bronchial divisions which were soft to feel and easily compressed, a marked contrast to the normal controls. Serial histological examination disclosed that the cartilage was deficient or absent along the walls in most cases from the third division down, but in small numbers was present in the angle of bifurcation of the bronchi. This deficiency in cartilage in the bronchial walls readily explains the physiological defect observed under the x-ray screen.

The problem is whether this defect is a developmental one, or whether it is secondary to infection. The available evidence favours a primary developmental origin for the following reasons. The lesions were surprisingly uniform, involving almost the entire bronchial tree from the second or third segmental division downwards. The principal defect in the structure of the bronchial wall was in the amount and distribution of cartilage. Had the cartilage been destroyed by inflammation, other structures would almost certainly have been affected, e.g. muscle and elastic tissue, but there was little evidence of this. Again, if inflammation had caused dissolution of cartilage in the walls of the bronchi, one would expect to find several bronchi in which no cartilage at all was present. In fact, however, in all cases where a division occurred one could find a small piece of cartilage at the bifurcation, although the walls themselves remained deficient. Examination of the bronchograms shows a 'nipping in' at the site of branching of the bronchi,

corresponding presumably with this small piece of cartilage.

In acquired bronchiectatic lesions cartilage destruction rarely extends up to the first and second segmental divisions, and then never in a uniform manner. Several patients examined in the present group soon after the onset of the disease showed gross bronchographic changes. The duration and the severity of the clinical infection was too short and too mild to result in such gross structural changes in the bronchial walls or to destroy the cartilage and cause 'flapping' during respiration. In no single case of bronchiectasis due to acquired disease have we seen changes comparable with those in these patients. We therefore presume that the cartilaginous defect is a developmental one and that the symptoms of chronic cough, wheezing, febrile episodes and later pulmonary emphysema, pulmonary hypertension and respiration failure in two patients were consequent on chronic secondary infection in the bronchiolar tree.

Summary

Five children with an unusual type of generalized bronchiectasis are described.

The clinical features of chronic cough, wheezy breathing and febrile attacks associated with widespread clinical signs in the chest and pulmonary emphysema were easily confused with asthmatic bronchitis, or chronic non-specific bronchiolitis or fibrocystic disease of the pancreas.

The clinical and radiological features in the five patients and the morbid anatomical findings in one suggest that the underlying basis is maldevelopment in the cartilage of the bronchial tree.

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APPENDIX

The lungs of five children of approximately the same age as Case 5 were examined by macroscopic dissection and by serial section of segmental bronchi and their divisions to establish a normal pattern for children of this age group (Gray (1954), Hayek (1953), Miller (1937)). The results are summarized below.

Macroscopic Findings

Method. Fixed lungs were dissected with fine scissors commencing at the segmental bronchus, which was called the first division bronchus (see Fig. 9). Any branches arising from this were counted and the dissection was carried as far as possible into the periphery of the lung.

Findings. The number of divisions of any segmental bronchus depended on the distance between the origin of the bronchus and the lung tissue it supplied. It was greater in longer bronchi than in short, e.g. lingula, with 10 macroscopically visible bronchial divisions, and pectoral, with five to six macroscopically visible bronchial divisions.

Divisions were of two types. Larger bronchi arose at a very acute angle. Small bronchi generally arose at a much greater angle from the parent trunk (lateral bronchi of Hayward and Reid, 1952).

The concept of an axial bronchus (Hayward and Reid, 1952) was not always easy to demonstrate. True dichotomous branching was common, the resulting bronchi being of similar calibre and coursing to the

periphery, each giving off approximately the same number of divisions (see Fig. 5b).

In general, however, a main or 'axial' bronchus could be followed from which lesser bronchi arose.

The bronchi in the fixed state were firm and elastic.

Circumferential cartilage plaques were present in all segmental bronchi and distally for three to six divisions, depending on the length of the axial bronchus.

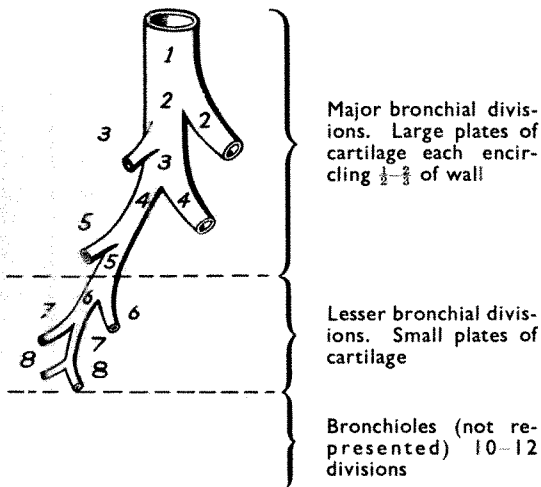
Isolated cartilage plaques occurred in the walls of bronchi from the fourth to the tenth divisions, although they were difficult to see in the more peripheral divisions and their presence had to be confirmed by histological examination.

Microscopic Findings

Serial sections were examined in continuity and all the branches arising from an axial bronchus were counted and an accurate assessment made of their cartilage content. The findings confirmed those made macroscopically.

Mucosa. Regular ciliated columnar epithelium pseudostratified down as far as the smaller bronchioles when it tended to become simple columnar in type. Mucosa rested on a condensed layer of collagen and merged with the underlying collagen network around mucous glands, muscle and cartilage.

Muscle. This occurred in regular fasciculi beneath the mucosa and varied in thickness with the bronchi exam-



L. Post Basic Br.

FIG. 9—Sketch of a typical normal bronchus and its divisions. Diagram shows method of numbering bronchi and distribution of cartilage in them.

ined (from 50μ up to 500μ). Muscle composed only a small portion of the thickness of the walls of the larger bronchi ($\frac{1}{8}$ to $\frac{1}{10}$) and slightly more ($\frac{1}{4}$ to $\frac{1}{2}$) of the more distal divisions.

Cartilage. In the larger bronchi (in general divisions 1-6) this was present as large plaques each partly encircling the lumen (so-called circumferential cartilage plaques). Their thickness varied greatly, being greater

the larger the bronchus, and generally ranging from $300-1,000\mu$ (Fig. 6b).

In the lesser bronchi (axial divisions distal to the fourth or fifth, and most of the lateral bronchi) the cartilage was distributed sporadically in the wall as isolated bars joined by a condensation of collagen and elastic fibres. A cross-section of such a bronchus would reveal two to four small plaques around the circumference. Their thickness averaged $100-300\mu$. Such cartilage plaques could be found distally as far as the sixth to tenth division, depending on which segment was being examined.

Bronchioles. The transition from bronchus to bronchiole was usually clear. Two criteria were used (a) cessation of cartilage, and (b) relation to surrounding lung. Thus, bronchi were always surrounded by a condensate of collagen in which ran several vessels, lymphatics and nerves, whereas bronchioles lay in intimate relation with lung parenchyma and lacked this collagenous mantle (Engel, 1947). In general the small peripheral bronchi contained cartilage in their walls, but this was felt to be a less reliable criterion than the latter.

On these criteria bronchiolar divisions numbered 10-12 in most cases.

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SYMMETRICAL PERIPHERAL OEDEMA IN INFANTS

BY

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Oedema is a common occurrence in newborn infants, particularly when they are premature. The seven patients, brief clinical accounts of whom appear below, appear to fall into a separate group.

Case Reports

Case 1. A male child was born in 1949 at term following a normal pregnancy and labour. His birth weight was 9½ lb. Swelling of the feet was noted soon after birth. He was breast fed for two months and then reared on dried milk.

On examination at the age of 6 weeks symmetrical pitting oedema of both feet extending a short distance up the legs was present. The hands were spared and no other abnormalities were found. B.P. was 80/50.

INVESTIGATIONS. Urine was repeatedly negative for albumin and deposit.

Hb was 70%, R.B.C. 3,500,000 per c.mm., W.B.C. 12,600 per c.mm. (neutrophils 44%, lymphocytes 49%, eosinophils 2%, monocytes 6%).

Plasma proteins were 6.5 g. per 100 ml. (albumin 4.6 g. per 100 ml., globulin 1.9 g. per 100 ml.). Blood urea was 30 mg. per 100 ml.

Biopsy from the dorsum of the foot showed that the epidermis was rather thin with oedema. The rete pegs were somewhat diminished and the corium a little thickened with some increase of collagen. There was slight perivascular infiltration with lymphoid cells.

The oedema had vanished by the age of 18 months, while growth and development proceeded normally. When last seen at the age of 8 years the child was obese, weight 100 lb. (mean 59½ lb.), height 55 in. (mean 50 in.), but was otherwise normal.

Case 2. This girl was an only child, although the mother had had two previous miscarriages. She was born in 1950, two weeks prematurely, after an uneventful pregnancy with a birth weight of 6 lb. The mother was stated to have had slight swelling of the left foot all her life, and her mother was said to have had oedema of the feet for many years. No swelling was found in the case of the mother, and the grandmother had bilateral but unequal oedema of the feet associated with varicose veins. Both women appeared otherwise healthy.

On examination at the age of 6 weeks the child was healthy apart from symmetrical pitting oedema of the

feet and lower legs, which tapered off about half-way to the knees. The hands were affected to a lesser degree.

INVESTIGATIONS. Urine was free from albumin and abnormal deposit and there was no abnormal amino-aciduria.

Hb was 80%, R.B.C. 4,500,000 per c.mm., W.B.C. 11,200 per c.mm. (neutrophils 43%, lymphocytes 51%, monocytes 6%). Blood urea was 35 mg. per 100 ml., blood calcium 11.2 mg. per 100 ml., serum phosphorus 5.6 mg. per 100 ml. Plasma proteins were 6 g. per 100 ml. (albumin 4 g. per 100 ml., globulin 2 g. per 100 ml.).

The oedema finally disappeared at the age of 4 years. She remained healthy apart from pneumonia when 7 years old. When seen at the age of 8 years a scraping of the buccal mucosa showed a female chromatin pattern. She was small, weight 46 lb. (mean 58 lb.), height 45 in. (mean 49½ in.), and the only other abnormality found was dystrophy of the little toenails. Bone age at this time was one to two years behind the chronological age.

Case 3. This girl, a third child, was born in 1951, the older two siblings being normal. She was said to have been born at term, but weighed only 4 lb. 11 oz. at birth. Pregnancy and labour were normal. Her feet and hands were noticed to be swollen at birth. She was fed from birth on dried milk.

When examined at the age of 2 months she weighed 7 lb. 2 oz. She had symmetrical pitting oedema of the feet and lower parts of the legs and the hands. There was slight webbing of the neck, a low hair-line, high arched palate and rudimentary nails. Signs of coarctation of the aorta were present.

INVESTIGATIONS. Urine was repeatedly normal. Blood urea was 38 mg. per 100 ml., serum cholesterol 135 mg. per 100 ml. Wassermann reaction was negative, and a chest radiograph was normal. Radiological bone age was normal (aged 7 years). A scraping of the buccal mucosa at the age of 6 years was chromatin-negative, suggesting the male sex.

When last seen at the age of 7 years she was mentally retarded and was attending an occupation centre. Her height was 44 in. (mean 47 in.) and her weight was 48 lb. (mean 51½ lb.). The oedema of the hands disappeared in the first year, but that of the feet lingered until she was 5. The other abnormal features were more pronounced, and the chest was broad with widely spaced

nipples. The signs of coarctation of the aorta were present with blood pressure in the arms 150/90 while the femoral pulses were not felt.

Case 4. A female child was born in 1954, two weeks prematurely, after an uneventful pregnancy. Her weight at birth was 6½ lb. She is the third child and the two older children are normal. She was admitted to hospital at the age of 6 weeks on account of a respiratory infection.

On examination there was symmetrical pitting oedema of the feet and lower parts of the legs and of the hands and wrists, which the mother stated had been present from birth. In addition slight webbing of the neck was present and she had dystrophy of the toenails.

INVESTIGATIONS. Urine was normal with no abnormal amino-aciduria. Hb was 85%. The plasma proteins rose from a total of 4.8 g. per 100 ml. at 2 months to 6.5 g. per 100 ml. at the age of 1 year. On each occasion the electrophoretic pattern showed a normal proportion of albumin and globulin. Serum bilirubin was 0.3 mg. per 100 ml., serum alkaline phosphatase 21.5 K.A. units, thymol turbidity 1 unit, serum sodium 320 mg. per 100 ml., serum calcium 10.6 mg. per 100 ml., serum phosphorus 6 mg. per 100 ml.

Examination of a scraping of buccal mucosa showed that the chromatin pattern was of male type.

The oedema of the hands disappeared by the age of 12 months, but that of the feet continued until she was nearly 3 years old. With the passage of time other abnormalities became apparent, notably low hair line, 'shark' mouth, ear deformities, anti-Mongolian slant to the eyes and broad chest with widely spaced nipples. She has remained small and at the age of 3 years 11 months weighed 25½ lb. (mean 35½ lb.) and was 36½ in. in height (mean 39½ in.). The blood pressure has always been normal and the bone age has corresponded with the chronological age.

Case 5. This boy was the third child of healthy parents. The two older siblings were healthy. He was born normally at term in 1954 after an uneventful pregnancy, his weight at birth being 7 lb. Symmetrical oedema of the feet and lower parts of the legs and, to a lesser degree, of the hands was noticed just after birth. The only other abnormality observed was dystrophy of the toenails.

INVESTIGATIONS. Urine was free from abnormal constituents and there was no unusual amino-aciduria. Hb was 90%, W.B.C. 6,500 per c.mm. (neutrophils 45%, lymphocytes 45%). Blood urea was 34 mg. per 100 ml. and the plasma proteins varied from 5.9 g. per 100 ml. at 2 months of age to 6.9 g. per 100 ml. at 8 months. The albumin/globulin ratio and electrophoretic pattern were normal on each occasion.

Biopsy from the dorsum of the foot showed rather thick epidermis with somewhat marked keratinization. The corium showed no inflammatory reaction.

Examination of a scraping of the buccal mucosa showed a chromatin pattern of male type.

Since then he has developed normally and the oedema finally disappeared by the age of 3½ years. At 4 years of age he was small, weighing 31½ lb. (mean 37½ lb.) and

his height was 36½ in. (mean 40 in.). The bone age was equivalent to his chronological age and the highest blood pressure recorded was 90/50.

Case 6. The only child of healthy parents, this girl was born in 1955 at term after a normal pregnancy and labour, her birth weight being 8½ lb. Symmetrical pitting oedema of the feet, lower legs and hands was noted at birth. The only other abnormalities found were a defect of the left pinna and dystrophy of the toe-nails, especially of the little toes. She was fed on dried milk from birth.

INVESTIGATIONS. Urine was repeatedly free from albumin and abnormal deposit and amino-aciduria was normal for her age.

Blood urea was 40 mg. per 100 ml., serum sodium 310 mg. per 100 ml. and serum potassium 22 mg. per 100 ml. The plasma proteins were 5.9 g. per 100 ml. (albumin 3.9 g. per 100 ml., globulin 2.0 g. per 100 ml.). The electrophoretic pattern was normal and the Wassermann reaction was negative.

The chromatin pattern from a scraping of buccal mucosa suggested the female sex.

At the age of 2 weeks adrenocorticotrophin, 10 units of the gel daily, was tried. This was stopped after three days as the oedema became more marked.

She has since developed normally both mentally and physically. Her blood pressure has never been raised, and when last seen at the age of 3 years 2 months it was 90/50. At that time she weighed 35 lb. (mean 31 lb.) and her height was 36 in. (mean 37½ in.). The oedema of the feet was still present though less marked. That of the hands had cleared by the age of 3 years. Her bone age was normal.

Case 7. This girl was the fifth child of healthy parents; the four elder siblings were quite healthy. She was born in 1955 at term, birth weight 5 lb., following a normal pregnancy and labour. Swelling of the feet was noticed at birth and the hands were stated to be swollen at intervals. She was fed on dried milk from birth.

On examination at 2 months of age she had symmetrical pitting oedema of the feet extending about half-way up the legs towards the knees. Mild pitting oedema of the backs of the hands was also present. In addition slight cyanosis of the nail beds and dystrophy of the toe-nails were seen. No other abnormalities were found.

INVESTIGATIONS. Urine was repeatedly free from albumin and abnormal constituents and there was no unusual amino-aciduria.

Hb was 85%, W.B.C. 6,500 per c.mm. (neutrophils 50%). Blood urea was 40 mg. per 100 ml., serum cholesterol 120 mg. per 100 ml., E.S.R. 12 mm. in one hour (Wintrobe). The plasma proteins were 6.4 g. per 100 ml. (albumin 4.2 g. per 100 ml., globulin 2.2 g. per 100 ml.). The electrophoretic pattern was normal.

A skin biopsy from the dorsum of the foot showed hyperkeratosis and mild parakeratosis with slight acanthosis. The deepest vessels of the corium were invaded by an infiltrate of tissue cells, a few plasma cells and neutrophils.

A scraping of the buccal mucosa was taken at the age of 2 years. The chromatin pattern was of male type.

When last seen at the age of 3 years 4 months her height was 31½ in. (mean 38 in.) and she weighed 23½ lb. (mean 33½ lb.). Her blood pressure was 100/60. The bone age was normal. Slight oedema of the feet only remained.

All these children had one feature in common, namely oedema, always of the feet and usually to a lesser degree of the hands, which had been present from birth. Pitting was always present and there was no discolouration of the skin nor evidence of circulatory disorder. The swelling of the lower extremities presented a rather typical appearance, being most marked over the dorsa of the feet. It tapered away up the legs to finish below the knees, resembling well-fitting field boots. It was always symmetrical. The oedema tended to disappear from the hands first, and to vanish from the legs in the first few years of life. In five children it has disappeared completely, while in two, both aged 3 years, it is still present but decreasing.

The marked similarity of the swelling without constitutional upset in all these seven patients suggests that all are suffering from the same disease, which has not occurred in other members of their families. In one instance the mother and grandmother were said to have suffered from swelling of the feet but no oedema was found in the case of the mother while the grandmother's oedema was associated with varicose veins, quite unlike the self-limiting disease seen in these children.

Of these seven children, five were undersized for their age when examined in later years. Despite the inferior growth, in only one of them was there a retardation in bone age (one to two years at the age of 8).

Five showed dystrophy of the toenails. This was confined to the toes and was most marked in the little toes. It was always symmetrical. The nails were small, deformed and had a brown hue.

Finally, in three of the five girls examination of the chromatin of the cells in a scraping of buccal mucosa showed the nuclear sex to be male. In the other two girls and the two boys the chromatin pattern corresponded with the morphological sex.

Discussion

The usual causes of oedema in the young infant can be dismissed. There was no evidence of heart or kidney disease, and prematurity was not a factor. Hypothermia was not seen and arthritis was not a feature.

Besides these well-known types of oedema the

earlier literature contains records, often in the form of single case reports, of oedema involving the extremities of newborn children. Confusion resulted from the use of such terms as 'trophic' and 'lymphangiectatic' oedema, 'scleroedema' and 'elephantiasis'.

Three names are particularly associated with these early accounts.

Nonne (1892) described a family with swellings of the lower limbs which were firm, fleshy and non-pitting (congenital hereditary elephantiasis).

Milroy (1892) gave an account of 22 persons among 97 members of one family with congenital 'trophic' oedema of the extremities. The condition was hereditary, permanent and unaccompanied by constitutional disease. The oedema affected one or both legs and might extend up to Poupart's ligament but not beyond. In 21 of the 22 cases the condition was present at birth.

Meige (1898) wrote of a family of eight, whose members suffered from chronic oedema of the legs. The condition was not congenital and usually appeared at about puberty.

Volz (1938) gave a summary of the literature on oedema of the newborn baby up to that time, and described an infant similar to those described here. In addition his patient had bilateral epicanthus and loose skin at the nape of the neck. He listed 12 other somewhat similar cases recorded up to that date.

From this clinical medley Mason and Allen (1935) differentiated one group which they called congenital simple lymphoedema. They described five patients in each of whom the oedema was congenital, affected one limb only and was persistent. The unilaterality and non-familial incidence differentiated them from congenital, familial lymphoedema or Milroy's disease, of which they confessed they had yet to see an example.

The histological features of their cases were characteristic. The subcutaneous fat was replaced by enlarged lymphatic vessels and by fibrous tissue.

These features exclude such a diagnosis in these seven children in whom the oedema was always symmetrical and in whom biopsy failed to reveal the characteristic findings.

Bonnevie (1932, 1934) showed that multiple malformations of the head and extremities appeared as a recessive trait in a race of x-rayed mice—Bagg-Little strain (Bagg and Little, 1924). She showed that these deformities arose as a result of the excessive escape of cerebrospinal fluid through the anterior foramen, an opening in the roof of the fourth ventricle. This excess fluid accumulated as myelencephalic blebs in the neck and then migrated

under the epidermis and eventually reached the extremities. Abnormalities resulted from the effects of pressure caused by these accumulations.

Ullrich (1936) adapted this theory to explain a number of apparently unconnected congenital defects in the human being. These were particularly unilateral deficiency of the pectoral muscles and motor cranial nerve defects as well as various abnormalities of the hand (club-hand). They were attributed to arrest in the migration of myelencephalic blebs. He also considered that unilateral webbing of the neck, congenital lymphangiectatic oedema and certain other defects, such as dystrophic nails and hypoplastic nipples, should be included in the wandering bleb hypotheses. These abnormalities were grouped together as the status Bonnevie-Ullrich, asymmetrical type.

In succeeding years this conception was expanded and, under the title of symmetrical status Bonnevie-Ullrich, a number of seemingly diverse defects was assembled. The most important of these was bilateral webbing of the neck (pterygium colli) accompanied by low hair line, preference for the female sex, loose skin, epicanthus, sagging eyelids, 'shark' mouth, abnormalities of the ears, high arched palate, cubitus valgus, defects of the nails, some degree of dwarfism and sexual infantilism, 'mushroom' epiphyses of the long bones, increased digital markings of the skull and oedematous swellings of the neck and extremities at birth which tend to disappear with the passage of time (Ullrich, 1949). Ullrich has since conceded that the wandering bleb hypotheses can no longer be regarded as applicable to the symmetrical, as opposed to asymmetrical, type of the status.

Independently Turner (1938) described seven girls from 15 to 23 years of age, each of whom showed a triad of infantilism, webbing of the neck and elbow deformity. As Ullrich remarked, these features comprise only some of the characteristics included by European authors in the symmetrical form of status Bonnevie-Ullrich. Yet writers of the English-speaking nations commonly refer to this complex as Turner's syndrome.

In the last 10 years further additions to the status have been suggested (Rossi and Caffisch, 1951; Silver, Kiyasu, George and Deamer, 1953). Terminology has been varied and largely centred on the question of sexual infantilism. The latter has received much interest since the demonstration by Moore, Graham and Barr (1953) that the genetic sex of body cells may be determined by a study of the nuclear chromatin. Use of this technique has shown that the majority of the affected patients, though morphologically girls, are genetically of the

male sex and have gonadal hypoplasia. In children examination of sections of the skin or scrapings of the buccal mucosa have enabled a correct diagnosis to be made before the absence of the normal changes occurring at puberty would draw attention to the condition. Examples in early life have been described by Silver (1956) and Grumbach (1957). The patients of both these authors had oedema of the feet in early infancy, which gradually disappeared.

Grumbach remarked that there is a group of young patients of either sex with a varied number of congenital defects, as described by Ullrich and Turner, in whom testes or ovaries are present normally. In these children gonadal and chromatin sex correspond and normal secondary sexual changes occur at puberty. He suggested that these patients should be grouped under the title of Turner-Ullrich syndrome to differentiate them from those, nearly all female, who also have gonadal atrophy, usually with male sex chromatin, whom he would label simply as gonadal dysgenesis.

As might be expected in a syndrome combining so many different defects, many examples are incomplete. In three of the seven children described here the appearances came to be characteristic of the symmetrical type of the status. The demonstration of cytological male sex in morphological females showed that they belonged to the gonadal dysgenesis group. The oedema present in the other four was identical with that seen in these three. In addition some other of the described features, such as small size or dystrophy of the nails, were usually present, and it is suggested that they are incomplete forms of the status and should be included in the Turner-Ullrich syndrome.

Summary

Seven children, each of whom showed symmetrical peripheral oedema of the lower extremities and usually of the upper extremities to a lesser degree, are described.

Four of them are considered to be examples of the symmetrical type of status Bonnevie-Ullrich in incomplete form, while the remaining three, all girls, are examples of the more complete form, also known as Turner's syndrome or gonadal dysgenesis.

When children show this clinical picture it is advisable to determine the genetic sex by examination of the nuclear chromatin.

Thanks are due to Dr. A. G. Marshall for pathological investigations and to Dr. Alan Booth for radiological examinations.

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PAEDIATRIC PATHOLOGY CLUB

Proceedings of the Fifth Annual Meeting

The Fifth Annual Meeting of the Paediatric Pathology Club was held at Bristol on October 23 and 24, 1959. The meeting on October 23 was held at the Children's Hospital, St. Michael's Hill, when the chair was taken by Dr. Norman Brown. The meeting on October 24 was held at Southmead Hospital, when Dr. Frank Lewis was chairman. Dinner was taken at the Ashton Court Country Club. Forty-five members and guests attended the meeting.

Scientific Communications

EDWARD HALL (Liverpool). 'Primary Hyperoxaluria.' Eight cases of this condition occurring in three families were described and the histology illustrated. The familial nature of the condition was briefly discussed. (Further details of these families are to be published in this journal shortly.)

J. F. BOYD (Introduced by A. M. McDONALD, Glasgow). 'Adrenal Hypoplasia in Siblings.' The first child of healthy parents was admitted when 3 weeks old with a history of abdominal pain and vomiting. Intestinal obstruction was diagnosed and at laparotomy a volvulus of the small intestine was found and was undone successfully. Post-operatively vomiting continued; the patient's condition deteriorated and he died. Autopsy revealed hypoplastic adrenal glands.

The second child born four years later was also a boy and he was admitted when 9 days old with a history of persistent vomiting. No ante-mortem diagnosis was made, but the child was treated on the basis of an overwhelming infection with hydrocortisone and antibiotics. In spite of this his condition deteriorated and he died within 24 hours.

Autopsy revealed hypoplastic adrenal glands.

The paper described and compared the post-mortem and histological features in the two cases. The evidence suggested that in each case this was a primary failure of the adrenal glands rather than a pituitary failure.

AVINASH MITHAL (Introduced by JOHN L. EMERY, Sheffield). 'Postnatal Development of the Lung.' A study of the postnatal development of the terminal respiratory unit had been carried out which indicated that there is an increase in the number of alveoli following birth. There is a rapid increase in the production of alveoli during the first year after birth and a steady increase in the formation of alveoli throughout the whole of childhood.

Differential counts had been done on the respiratory tubes in the lung which suggested that there is an increase after birth in the number of small bronchioles and that slow progressive cartilagization of these bronchioles occurs during later childhood.

P. O. YATES (Introduced by F. A. LANGLEY, Manchester). 'Birth Injury to the Neck.' This paper was published in full in this journal (*Archives of Disease in Childhood*, 34, 436.)

KEITH ROGERS (Birmingham). 'Group F Haemolytic Streptococci as Pathogens in Children.' This group of streptococci is of importance in lesions connected with the whole gastro-intestinal tract, but the organisms demand a slight increase of CO₂ in the atmosphere in which they are grown, and a simple technical procedure was described to provide this.

EDITH FAIERMAN (Introduced by HUGH CAMERON, Birmingham). 'The Significance of One Umbilical Artery.' Eleven cases of single umbilical artery were encountered among 411 routine autopsies on stillbirths and live born babies of 8 weeks of age or less (an incidence of 2.7%).

Severe associated malformations were found in 81%, and in 23% of controls. The commonest malformation was of the lower urinary tract. There was a high incidence of stillbirths (45%) and of twinning (18%). In only one case was there an associated abnormality of the placenta. No correlation was found between the condition and maternal factors.

Absence of an umbilical artery can be diagnosed at birth by simple examination of the cord. In the absence of severe external malformations, such an infant has a 2:1 risk of internal malformations, which may require early surgical treatment.

G. S. ANDERSON (Newcastle). 'Pituitary Lesions Associated with Congenital Adrenal Hypoplasia.' Pituitary malformations in the absence of severe lethal malformations of the head are rare and comprise four published cases, all showing adrenal hypoplasia.

Three further cases were briefly described although one showed a cleft palate and other incidental abnormalities. The three infants died unexpectedly at 18, 23 and 33 hours and in all the adrenals were hypoplastic, resembling those in anencephaly. In one, a male, the pituitary grossly appeared absent but may have been ectopically placed in the sphenoid bone. The testes

were undescended and showed marked tubular and interstitial cell hypoplasia.

In the other two cases, both females, a small bean-shaped nodule of tissue was found in a small sella. Serial sections in both cases showed it to consist solely of pars anterior. In both cases there was a small rounded blunt knob of tissue in the region of the tuber cinereum which histologically was composed of malformed neurohypophyseal tissue anterior to which was a minute island of anterior lobe cells. In one case these cells apparently formed an attenuated connexion with the anterior lobe tissue in the sella.

It was suggested that the fundamental lesion in these cases was the pituitary malformation and that the adrenal hypoplasia was but one effect of this, although probably the most important.

H. B. MARSDEN (Manchester). 'Herpes Encephalitis following Fracture of the Skull.' A girl, aged 4 years, sustained a compound depressed fracture of the skull. There was excellent recovery for one week but on the eighth day pyrexia developed with convulsions and progressive coma. The child died 11 days later and at autopsy an inflammatory reaction was found in the brain involving the meninges and, in particular, the pons and basal ganglia. Perivascular cuffing and foci of inflammatory cells were prominent. An abundant growth of herpes virus in HeLa culture was obtained from the basal ganglia, the lung being sterile.

Evidence was produced to suggest that this was a case of herpes encephalitis, the virus probably entering at the site of the fracture.

The distribution and nature of the lesions were predominantly basal and cellular rather than destructive and unusual. Comment was made on the absence of Lipschütz bodies or type-A inclusions.

K. M. LAURENCE (Cardiff). 'The Pathology of Hydrocephalus.' The material seen between 1955 and 1958 at The Hospital for Sick Children, Great Ormond Street, London, was presented.

On the basis of the series, under-absorption was thought to be unproven, and over-production of C.S.F., seen in cases of choroid plexus papilloma, though interesting, was uncommon, while obstruction to the C.S.F. pathway was both pathologically and numerically the most important. Examples of aqueduct malformation were shown, most of which were found in association with other C.N.S. anomalies, notably spina bifida cystica and the Arnold-Chiari malformation. It was stressed that in cases of spina bifida cystica, the often associated hydrocephalus, although frequently due to malformation, was in many cases aggravated by, if not entirely resulting from, post-inflammatory lesions caused by ascending infection from the myelocoele.

Aqueduct gliosis, although rare, presented problems in aetiology. Because of its association with neurofibromatosis, it was suggested that, like neurofibromatosis, it might be hamartomatous in origin.

The purely inflammatory lesions formed about half the series. The various pathological changes, such as

aqueduct ependymitis leading to aqueduct block, and occlusive fibrosis of the arachnoid resulting in fourth ventricle exit foramen, or basal cistern block occurring singly or in combination, were illustrated by cases.

It was stressed that in over 60% of this group bleeding into the C.S.F. pathway at the time of delivery was regarded as the aetiological inflammatory agent, though in some cases little evidence of bleeding could be found at the time of the autopsy. (In discussion several members said that this series is a highly selected group and does not represent the hydrocephalus seen generally in the country.)

H. URICH (London). 'Some Remarks on the Neuronal Lipidoses.' All neuronal lipidoses share the characteristic feature of accumulation of lipids in the cytoplasm of nerve cells in addition to storage in other organs. Six diseases of this group were studied in Dr. R. M. Norman's laboratory in Bristol (see Table). Contrary to some of the older teaching based on superficial similarities, these diseases constitute separate entities distinguishable both histologically and by chemical analysis.

The conditions most commonly confused are Tay-Sachs' disease and Niemann-Pick's disease, despite the differences in the chemical composition of the brain in the two conditions. Examination of a case of Tay-Sachs' disease with exceptionally severe visceral involvement also revealed histological differences. The coarse vacuoles found in this case in reticulo-endothelial and glandular epithelial cells were apparently empty in formalin-fixed material, while in Niemann-Pick's disease the stored lipid could be easily stained with haematoxylin lakes.

Batten's disease (juvenile amaurotic idiocy) differs from Tay-Sachs' disease in the absence of an excess of ganglioside in the brain. The lipid stored in reticulo-endothelial cells of some cases is histochemically similar to that found in the neurones. It has not been identified chemically.

Gargoylism can be distinguished from the amaurotic idiocies by the involvement of connective tissues including the meninges and the adventitia of cerebral blood vessels.

In infantile Gaucher's disease only a few nerve cells show unequivocal signs of storage while others undergo degeneration without preceding storage. This phenomenon also occurs in other neuronal lipidoses and may be illustrated by the atrophy of the granular layer of the cerebellar cortex in Batten's disease.

The inclusion of metachromatic leuco-encephalopathy in this group is based on the finding of storage of sulphatide in numerous neurones of the basal ganglia, brain stem, spinal cord and posterior root ganglia. Severe demyelination, which is the most striking feature of this condition, may also be found in other neuronal lipidoses, particularly in cases of Tay-Sachs' disease with a protracted clinical course.

Neuronal storage, degeneration of nerve cells and loss of myelin sheaths may all be interpreted as results of the various disorders of lipid metabolism, presumably enzyme deficiencies, characteristic of these diseases.

THE NEURONAL LIPIDOSES

	Localization of Storage		Predominant Stored Substance	
	Neuronal	Visceral	Neuronal	Visceral
Tay-Sachs' disease	Ubiquitous	(Glandular parenchyma R.E. system)	Ganglioside	? (Polysaccharide)
Niemann-Pick's disease	Ubiquitous	R.E. system, glandular parenchyma	Sphingomyelin	Sphingomyelin
Batten's disease	Widespread	(R.E. system)	?	?
Gargoylism	Widespread	Connective tissue, glandular parenchyma R.E. system	?	Polysaccharide
Infantile Gaucher's disease	Minimal	R.E. system	?	Cerebroside
Metachromatic leuco-encephalopathy	Limited	Kidney, bile passages	Sulphatide	Sulphatide

R. M. NORMAN (Bristol). 'Intracerebral Calcifications.' The histological evidence pointing to a vascular factor in the pathogenesis of cerebral calcification was illustrated by reference to cases of the Sturge-Weber syndrome and of symmetrical cerebral calcification. In the former condition the calcifications tend to be localized in the outer layers of the cortex, that is, near the meningeal angiomas, but they are also seen in certain deeper laminae, notably the fourth layer of the calcarine cortex. In symmetrical cerebral calcification, whether associated with parathyroid deficiency or with familial microcephaly, the cortical calcifications have a predilection for the deeper parts of the gyral walls, especially in the boundary zones between major arterial territories. The fourth layer of the calcarine cortex may also be selectively affected. In the basal ganglia the localization of the calcifications is very similar to that found in status marmoratus following birth injury, though the lesions are otherwise dissimilar. The common factor appears to be a selective vulnerability of the capillaries of the affected areas.

The following short papers and cases were also presented:

KENNETH RHANEY (Dundee). 'Hypertrophy of the Choroid Plexus.' A full-term female foetus with gross hydrocephalus was delivered with difficulty after craniotomy. The trunk and limbs were normally developed and nothing of interest was found in the thoracic and abdominal viscera.

The head was greatly enlarged although the bones of the vault showed premature synostosis and the fontanelles were not enlarged. Reconstruction of the damaged brain showed that the septum lucidum, fornix and most of the corpus callosum were absent and that the lateral and third ventricles formed a single chamber. The lateral ventricles were greatly dilated; they were enclosed by a thin shell of cortex and atrophic white matter and their ependymal surface was coarsely nodular. Posterior to the genu the corpus callosum was replaced by a thin membrane which lined a large sac. This sac lay between the cerebral hemispheres posteriorly and formed part of the common ventricle.

The whole choroid plexus in the common ventricle

formed a large tumour with a rough irregular surface. On histological examination it showed the classical structure of a simple choroid papilloma.

The brain stem and cerebellum showed no abnormality. The aqueduct was of normal size, and the foramina of the fourth ventricle were patent. The leptomeninges showed recent haemorrhage but no other macroscopic abnormality.

The papillomatous choroid plexus appeared to be responsible for ventricular dilatation. It may well have produced an excess of cerebrospinal fluid and also given rise to obstruction.

LESLIE WHITE (Manchester). 'Cushing Syndrome associated with Suprasellar Tumour in an Infant.' A male infant of 3 months presented with typical Cushing syndrome. There was sudden deterioration after 17 days with death. Autopsy revealed a large suprasellar tumour and bilateral adrenal hypoplasia with terminal thrombosis of the galenic veins. The tumour, which was continuous with a normal size pituitary gland, had an undifferentiated lobular epithelial structure. Some evidence of basophil cell origin was obtained.

A. M. McDONALD (Glasgow). 'Krabbe Type Diffuse Cerebral Sclerosis.' A female, aged 9 months, was admitted the day before death severely ill with bronchopneumonia; she had been brownish-yellow at birth and for the following two months. At 7 months of age she had not sat up; she was a fat, mentally deficient child and her eyes did not follow light. Skull circumference was 43 cm., and she had a large anterior fontanelle.

At autopsy a Krabbe type of diffuse cerebral sclerosis, bronchopneumonia, gastric ulcers and oesophagitis were found.

A. M. McDONALD (Glasgow). 'Congenital Absence of Biliary Ducts.' A premature male baby with complete harelip and cleft palate developed jaundice and white stools at the age of 7 weeks. Liver function tests suggested an obstructive type of jaundice.

A cholangiogram showed free passage of contrast medium into the duodenum through the common bile duct. The hepatic duct was faintly outlined and small in calibre.

At biopsy the liver was olive green. Histological examination showed that biliary ducts were either absent or in very small numbers. Biliary thrombi were also in small numbers. Early fibrosis was equivocal. The lesion was considered to be a bile duct atresia at the ductal level and it was thought that cirrhosis would follow.

The child is now 10 months old, is very well and not jaundiced. The cleft palate is about to be repaired.

E. HALL (Liverpool). 'Ganglioneuroblastoma. An Unusual Presentation.' A case of extra-adrenal abdominal ganglioneuroblastoma in a 2½-year-old boy who presented with severe diarrhoea and some vomiting. There was a striking cessation of symptoms after removal of the tumour. Attention was drawn to a small number of similar cases recorded in the literature, and the possibility that a minority of these tumours may have internal secretory effects was discussed.

IAN DAWSON (London). 'Adenocarcinoma of the Testis in a Child of 11 months.' A Jewish child of 11 months developed a gradual, apparently painless swelling in the left testis over a period of two months. Both testes were present in the scrotum. A left orchidectomy was performed.

The testes measured 3×2×1.5 cm. and appeared completely replaced by yellowish, rather gelatinous tissue. The epididymis appeared to be intact.

The histological appearances were uniform throughout all the blocks. The tumour consisted of irregularly arranged gland acini which varied in size from small solid elements to irregular spaces, into some of which papillary processes projected. The epithelium was in places cubical, in places low columnar. The acini were separated by loose oedematous stroma.

This tumour falls into the group of those described by Magner (1956) and may be called an adenocarcinoma of infant testis. The source of the growth remains uncertain but may be rete or junctional tubules.

(Several members of the club had seen similar tumours.)

R. L. HOLMAN (Introduced by G. OSBORN). 'Persistence and Overgrowth of Immature Blastema in Both Kidneys of a Premature Infant.' A female infant born of 32 weeks gestation who survived 13 hours. Death was due to respiratory insufficiency; the lungs were only partially expanded and haemorrhagic.

Both kidneys were greatly enlarged; each weighed 70 g. and measured 7.0×3.5×3.5 cm.; the cut surfaces showed replacement of normal structure by irregular cream and brown areas. The capsular surface showed a moderate degree of lobulation.

Microscopically both kidneys showed widespread persistence and overgrowth of immature blastema tissue

interspersed and mingled with smaller zones of normally differentiated renal tissue. Immature blastema showed all gradations from undifferentiated deeply basophilic round cells through developing tubules and glomeruli to moderately well defined structures. A moderate number of mitoses were present in many such areas. There were many large straight tubules, probably all collecting tubules, extending radially from the medulla through the immature cortical zone almost to the capsule. Many of these were dilated, especially where they branched. Some collecting tubules ended in relation to zones of immature blastema tissue. Terminal collecting ducts were largely of normal appearance and lined by transitional cells distended with glycogen. No heterotopic tissues such as skeletal muscle and cartilage were found.

The diffuse nature of the anomaly in these kidneys suggests some generalized failure of organization of normal development rather than a localized overgrowth of metanephric blastema, such as occurs in a nephroblastoma.

HUGH CAMERON (Birmingham). 'Angioma of Larynx in Laryngeal Stridor.' This paper concerned three infants with severe persistent laryngeal stridor which did not respond to medical treatment or tracheotomy. All showed severe laryngo-tracheitis at autopsy and a small submucosal capillary haemangioma of the sub-glottis. These angiomas may be missed unless particularly careful examination is carried out and they appear to be more common in intractable laryngeal stridor than is usually recognized.

DOUGLAS BAIN (Edinburgh). 'Congenital Leukaemia.' Two cases of congenital leukaemia were described, one of which was presented at birth with nodules in the skin. There was no history of mongolism or of radiation during pregnancy.

JOHN L. EMERY (Sheffield). 'Chronic Rectal Ulcer in Boy of 14.' A chronic indurated bleeding ulcer situated in the anterior wall of the rectum which was probably basically an angioma.

G. S. ANDERSON (Newcastle). 'Pinhole Perforation of the Foetal Colon.' A child with meconium peritonitis due to perforation of the colon, apparently due to a local defect in musculature.

A. M. McDONALD (Glasgow). 'Umbilical Polyp.' An 11-month-old male infant presenting with an umbilical polyp. Since the cord separated a small black lump had been present in the umbilicus. Histology showed the features of a simple pigmented naevus, the colour being due to excessive melanin.

BOOK REVIEWS

Helping Your Child to Get Well. Ed. LEN CHALONER. By SIMON YUDKIN, J. LANGRIDGE, PHYLLIS WOOLRICH and LEN CHALONER. (Pp. 142; 31 figs. 16s.) London: Allen & Unwin. 1959.

This book is full of sound common sense. It is not intended to be a family doctor but information on some diseases is given for which the child would be nursed at home. It is in three parts. The first deals with observation and the nursing of sick children at home. It is written in such a way that it makes for a good patient-doctor relationship. The second part gives good advice on providing interests for children of all ages who are confined to bed. The suggestions are useful and inexpensive. The third part discusses the problems arising when a child has to go into hospital. The book can be highly recommended but it seems a pity that the price is so high.

The Child with a Handicap. Edited by EDGAR E. MARTMER. (Pp. xxiv+409; illustrated; 82s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

Although the preface states that this book 'is not primarily a medical text' but is designed for 'a more general public', there is much in it to profit family doctors, school doctors and paediatricians.

The main part of the book is composed of 15 chapters contributed by individual experts on all the usually accepted childhood handicaps, poliomyelitis, cerebral palsy, visual defects, speech and hearing defects, muscular dystrophy, mongolism, as well as some of the less common handicaps such as familial dysautonomia and amputations.

Each of these chapters is a clearly written guide to the background and clinical definition of a specific handicap. The effects of the handicap are explained and treatment as well as general management of the child are detailed.

Special note is made of the various agencies concerned in medical and surgical care, physiotherapy, schooling, occupational training and guidance in choosing a career.

Five of the chapters are illustrated and most contain references to recent work, especially to recent articles in paediatric literature.

The first five chapters are separate essays, defining the part played by the members of 'The Team' in the management of the disabled child. The points of view of the parent, the physician, the psychiatrist, the teacher, and the social worker are given equal prominence.

A chapter on the Role of Adoption Agencies is somewhat unexpected in a book of this sort, but makes clear the readiness of would-be adopting parents in the United States to accept children with a variety of handicaps.

The following chapter on Heredity Counselling gives examples of family situations in which such discussion had been very important.

The final chapters are a series of short guides. Besides lists of play, reading and education materials, they include in 'Guides for Discipline' and 'Guides for Parents' two short, thoughtful essays on the general management of any disabled child.

Although the book has 27 contributors, the Editor has been successful in obtaining a high level of clarity in the descriptions of the various disabilities, of modern methods of management, and of the many agencies involved.

Whilst some of the chapters are directed chiefly to the parents of handicapped children, much of the clinical detail would seem, to a reviewer working in the British Isles, to be far beyond the requirements of the average parent. The book's principal value lies in its wide view of the whole field of handicapped children and its very clear presentation of the details of so many disabilities. It should be read by all who have any part in the clinical, educational or administrative care of any child with a handicap.

Diagnosis of Congenital Heart Disease, 2nd ed. By SWEN R. KJELLBERG, EDGAR MANNHEIMER, ULF RUDKE and BENGT JONSSON. (Pp. xiv+866; 727 figs. \$28.00) Chicago: The Year Book Publishers, Inc. 1959.

The second edition of this important diagnostic manual of congenital heart disease closely follows the pattern of the first and is based on a detailed analysis of material seen at the Karolinska Hospital in Stockholm, now swollen to 742 cases. It is enlarged by four chapters, contains many amplifications and corrections as well as an increased number of illustrations.

In the 30 different abnormalities studied, six contain between 60 and 140 examples of each and between them comprise 80% of the total. They are patent ductus arteriosus, ventricular septal defect, coarctation, pulmonary stenosis, auricular septal defect and Fallot's tetralogy, in that order of frequency.

The first few chapters are devoted to the embryology of the heart, X-ray anatomy, techniques and to a brief summary of material to be studied. Thereafter each condition is taken in turn and the chapters follow each other in a repetitive pattern of clinical features and E.C.G., X-ray, electrokymography, cardiac catheterization, haemodynamics during exercise and angiocardiology. This list may be abbreviated for a few uncommon conditions but the arrangement never alters. Each condition is illustrated with a profusion of photographs, diagrams, tracings and charts. At the end of the

book there is a list of over 700 references with titles in full and an index which, though short, appears to function efficiently.

To the reviewer, an English-style consulting paediatrician without special cardiac training, of average intelligence but perhaps with difficulties regarding spatial relationships, this book is a revelation and has led to a revolution in the understanding of congenital cardiac disease. Every page and illustration bears evidence of imaginative effort spent in clarifying and elucidating problems relating to the action and haemodynamics of the heart working under abnormal conditions, and step by step each investigation is made to yield up its logical contribution to diagnosis. An important contributory factor to the character of this book is the impeccably simple and consequently lucid English in which it is written, which must reflect on both the original Swedish and on the translation.

The book sticks precisely to its terms of reference and diagnosis never spills over into prognosis, nor is there ever a hint that the subtle exposition of morbid anatomy, physiology and haemodynamics might have a bearing on treatment. But perhaps it would be greedy to ask for more: it is a fine book to have to refer to frequently.

Rheumatic Fever: Epidemiology and Prevention. Ed. R. CRUICKSHANK and A. A. GLYNN. (Pp. 193; 26 figs. 25s.) Oxford: Blackwell Scientific Publ. 1959.

In September, 1956, at the invitation of Professor R. Debré a conference was held at the International Children's Centre in Paris under the chairmanship of Dr. David Rutstein.

Experts from all over the world assembled to discuss the epidemiology and prevention of rheumatic fever. This record of the proceedings is arranged in sections, each of which is introduced by an acknowledged authority (R. Wahl, P. Hedlund, M. McCarty, E. G. L. Bywaters, M. Finland, P. Mozziconacci and Mlle J. Labesse), and each is followed by a series of short communications and a general discussion. Among a large number of distinguished delegates Bruce Perry, R. E. O. Williams and R. Cruickshank represented Great Britain.

This account contains a cross section of international opinion regarding the bacteriology and immunology of Group A haemolytic streptococci, including practical information about the isolation and recognition of these organisms and their antibodies. This is followed by a discussion of the epidemiology of streptococcal infections and their relationship to the development of rheumatic fever in certain individuals. This leads naturally to consideration of methods of preventing rheumatic fever.

After an interesting discussion by Finland on changes in the resistance of bacteria to antibiotics since 1949, a number of important points were raised. For example, although sulphonamides are suitable for prophylaxis of rheumatic fever since they are not bactericidal, they are quite unsuitable for treatment of streptococcal infections or for the prevention of first attacks. Penicillin is the most effective available agent, both for prevention and control of streptococcal infection. Unfortunately half

the attacks of rheumatic fever occur without any obvious sore throat and the diagnosis of rheumatic fever is still largely a matter of clinical judgment and application of the criteria laid down by Duckett Jones.

The proceedings of the Conference have been translated and edited by Professor R. Cruickshank and Dr. A. A. Glynn, who are successful in producing a readable and well balanced book.

The Artificial Feeding of Normal Infants. By WILLIAM EMDIN. (Pp. 113; 3 figs. 16s.) Howard Timmins. 1959.

It is not very long since the artificial feeding of infants was considered an exact science and books on the subject were bulky and their formulae complicated. As a result few students made any serious attempt to understand the problem and many practitioners have been content to leave it to their nursing associates or advised mothers to follow the instructions on the tin.

Since then the subject has been simplified and it is realized that most babies are very tolerant and will survive on almost anything approaching a normal feed. There can be no scientific exactitude in a subject where measurements are in teaspoons which from house to house vary in size and in how well they are filled.

A new difficulty has arisen, however, in the multiplicity of preparations now available for infant feeding and this book sets out to present 'a simple, practical feeding scheme applicable to feeding with natural cows' milk and all types of the proprietary milk products in common use'. In this it succeeds admirably and the principles laid down are those generally recognized by paediatricians as the most satisfactory.

The book is divided into three parts. The first considers artificial feeding in general, the second describes the use of the different preparations available, and the last is an up to date discussion on mixed feeding and the use of dietary supplements. The subject matter is clearly and simply presented and there are numerous valuable tables making for easy reference.

This is a most satisfactory book and one which I have no hesitation in recommending to students, nurses and practitioners.

A Manual of Paediatrics for South-East Asia. Edited by PINCHAS ROBINSON and ARVID WALLGREN. (Pp. xlx+464. Rs. 7.50.) Calcutta: Orient Longmans. 1959.

Although half the world's children live in the tropics and sub-tropics, the study of disease problems among them has been slow to gather momentum. Now, however, things are changing, and tropical paediatrics is becoming recognized as a subject worthy of world-wide study. Courses are being held, Chairs established, a journal is now flourishing, and finally the text-books have appeared.

This is the second book to have been published within the last two years, with two distinguished editors and 55

contributors. The editors criticize the first book on grounds of expense, and this book is a courageous attempt to reduce cost by the 'economy' standard of its production, and by virtually abolishing illustrations.

Such an attempt, however, is bound to be fraught with difficulties, and it must be confessed that this is rather an odd book. Its 440 pages of text are subdivided into a very large number of small essays with no attempt at grouping under common headings by system. The result is a volume, more readable than most text-books, but disconcertingly haphazard for the undergraduate at whom it is largely aimed. One feels that a little co-ordination and fusion of the many separate sections would produce a much more coherent book.

The question of format, however, is less important than that of content and balance, and this is where the book is most open to criticisms. A few instances will suffice. The section on rare muscular disorders is given almost as much space as the whole of the respiratory tract; coeliac disease and fibrocystic disease of the pancreas are together granted only half a page; and, strictly in a book designed to cover tropical paediatrics, there is something wrong when kwashiorkor is dismissed in one page, and the whole of infant feeding, nutritional disorders and vitamin deficiencies are given less space than the much rarer disorders of the endocrine glands. Whilst, too, it is quite legitimate, though perhaps unwise, to dispense with illustrations in a book of this sort, one wonders what purpose is served by including 13 only, four of them on one disease.

Taken individually, many of the sections are admirable. But the preface states the aim of the book as one 'which covers all or most aspects of child care as those appear in this part of the world, which includes the total field of paediatrics as taught in the West, and many other problems which are of little or no importance there'. This would be a very large claim for a much larger book, and is far from being realized here.

In its present form it is difficult to recommend this book as the sole paediatric text-book for undergraduates. But if in future editions the editors would expand those parts dealing with the tropical and preventive aspects, especially as they apply to South-East Asia, and reduce somewhat those sections on general paediatrics which are dealt with more fully in other books, the book would establish itself as a useful and interesting companion to a new and important subject.

Le Bien-Etre de L'Enfant en Afrique au Sud du Sahara.

By MAURICE GAUD. (Pp. 186.) Published by the Centre International de L'enfance, Lagos. 1959.

The publication commemorates and, to some extent, reports the proceedings of a six-day congress covering an immense field which was held in Lagos in March, 1959, under the Chairmanship of Professor Robert Debré. Delegates from European countries with African interests joined representatives from the territories themselves, the majority of whom held some administrative post. The participants are categorized

in the preface as sociologists, ethnologists, agronomists, psychologists, physical anthropologists, educators and specialists—in public health, sanitary education, growth, and juvenile delinquency. There were also observers from a number of political organizations. Scientific communications seem to have been concerned with correspondingly diffuse subject matter, without much integration, although the abstracts (in French and English) are too brief to provide much more than main headings. Valuable as this volume should prove as a memento for those fortunate enough to have attended the congress, it is unlikely to be of profit to a wider public, unless perhaps for the useful bibliography that concludes it.

Le Nouveau-né—Directives Therapeutiques Medico-chirurgicales. By MARCEL FÉVRE. (Pp. 190; Fr. fr. 2,500.) Paris: G. Doin et Cie. 1959.

This book is written for children's physicians by a surgeon, with the intention of showing them the indications for surgical intervention in the newborn. The author is professor of paediatric and orthopaedic surgery in the faculty of medicine in Paris and has already written a book about paediatric surgery for surgeons.

It is obvious on reading the book that he is a surgeon of wide experience and considerable skill. He keeps admirably to his self-imposed limits and does not discuss details of technique of no interest to physicians. The chapters cover conditions requiring immediate treatment, birth injuries, visible congenital defects, internal congenital defects, disorders of the post natal period and resuscitation. A wide range of conditions is covered in considerable detail. The methods described are modern and in most cases similar to those used in Britain; the chapter on intestinal obstruction is particularly good. The chief defect in the book is the lack of illustrations, necessary for the rare conditions described. There are a few adequate diagrams and a handful of very bad photographs. The book is paper-backed and uncut. The type used is admirable and there is a good index. The author deliberately limits his references to 18 standard works, although he names many more authors in the text (including 'Grey and Turner').

This is a good and unusual book which requires little knowledge of the French language and will provide all paediatric physicians with a good deal of new information.

Paediatric Tutorials: The Newly Born Infant. By

ANDREW BOGDAN. (Pp. 38; 3s.) Available from Anstick's Medical Bookshop, 53 Great George Street, Leeds 1, and other medical bookshops.

Dr. Bogdan has constructed a small notebook to be used at the cot-side. The main headings are filled in which deal with the normal and sick infant and ample blank pages are included for the student to make his own notes.

Skeletal Calcification and Phosphate Metabolism. By R. STEENDUK. (Pp. 163; 510 refs.) M.D. Thesis, Handels Drukeri J. Ruysendaal, Amsterdam.

The metabolic processes responsible for skeletal calcification revolve around the problems of calcium and phosphorus absorption and excretion, and the maintenance of the levels of these substances in the blood. The unravelling of these problems has always advanced as much by the study of rickets as from a direct study of ossification in healthy bone. This monograph, a university M.D. thesis, summarizes the modern concepts of these processes against an exhaustive and critical review of the literature (some 500 references are listed) supported by the author's own clinical and experimental observations in cases of primary resistant rickets and of the de Toni-Fanconi syndrome. The observations were designed to elucidate specific points regarding calcium metabolism and serum phosphate regulation and tubular reabsorption, around which so much that concerns bone formation appears to revolve.

In the first few sections the author traces the radical changes that have come over our ideas on the mineralization of ostioid; how the older ideas of precipitation from a supersaturated solution of minerals, and the importance of phosphatase, have become outdated and given place to the idea of crystallization of hydroxy-apatite of calcium on to an organic, preformed, mucoprotein template.

The rest of the monograph discusses extensively the biochemical and clinical aspects of the activity of vitamin D in relation to rickets, the extremely complex relationships that exist between calcium, phosphate, the renal excretion and retention of these two substances, the actions of vitamin D and parathyroid, and the rate of both calcification and the removal of mineral salts from bone.

With regard to the role of the renal tubules in the production of resistant rickets, whether primary or in association with amino-aciduria and glycosuria, he discards the theory of a phosphate diabetes, a primary failure of reabsorption of phosphate by the renal tubules as too simple and even misleading, and suggests that there is a failure at some point in the metabolic merry-go-round in which an equilibrium is normally maintained between (1) the availability of minerals for calcification; (2) the rate of calcification; (3) the serum phosphorus level; (4) the tubular reabsorption of phosphate; and (5) the solubility of bone salt. He considers that clinically the availability of calcium is probably the main conditioning factor in this equilibrium.

In the introduction the author complains, perhaps rightly, that clinicians are comparatively ignorant of the physiology of calcium and phosphorus metabolism, and he quotes Howard as stating that 'in the field of modern medical investigation, the clinician usually is placed at the bottom of the totem pole, beneath his colleagues versed in the basic science . . . though his opportunities for viewing the subject in its broadest sense are apt to be greater than those of the biochemists or physicists'.

Anyone willing and still able, for it is tough going, to spend a long week-end reading and digesting this monograph will find his grasp of the complications of calcium

and phosphorus metabolism brought firmly up to date, and the boundaries of his biological thinking considerably widened.

Involution of the Ductus Arteriosus. A Morphological and Experimental Study, with a Critical Review of the Literature. By A. SCIACCA and M. CONDORELLI. (Pp. 52; 25 figures. Sw. fr. 7.00.) Basel and New York: S. Karger. 1960.

This treatise first gives a critical review of the literature on the theories of the closure of the ductus arteriosus. There are some valid criticisms of the views of Barcroft and his colleagues; no mention is made of the work of Patten (1933), whose conclusions were the same as the authors'; and the more recent contributions of Adams and Lind (1957) and Dawes and his colleagues (1954) to our knowledge of the physiology of the foetal and neonatal circulation are not discussed.

There follows a description of the authors' morphological and experimental studies of the time of closure of the ductus in guinea pigs, which includes the effect of sudden interruption of the blood flow through the ductus and the pulmonary artery in the foetus and newly born animal, and also some angiocardigraphic studies. Their findings support those of Patten and point to a gradual development of the circulation through the lungs during foetal life, the pulmonary flow increasing as the ductal flow decreases. No light is thrown on the exact mechanism of closure of the ductus, but the authors believe it to be a gradual process.

There are interesting observations of the varying size of the ductus relative to the pulmonary artery at different stages of foetal development which may be significant in relation to differences in size and shape of patent ducts found in infants and children at operation and may give a clue to the time of a possible foetal insult responsible for the condition.

The study will be of particular interest to cardiologists and also to pathologists, physiologists and anatomists interested in this field.

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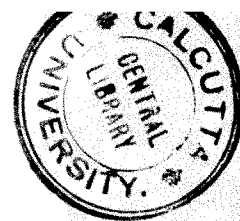
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Catalog of the Clifford G. Grulee Collection on Pediatrics.

Edited by HERMAN H. HENKLE. (Pp. viii+340. \$15.00.) Chicago: The John Crerar Library. 1959.

This book is beautifully produced and refers to Grulee's collection of over 4,000 publications which were given to the John Crerar Library in Chicago.

Anyone interested may consult the book in the library of the B.M.A.



HEAD INJURIES IN CHILDREN

OBSERVATIONS ON THEIR INCIDENCE AND CAUSES WITH AN ENQUIRY INTO THE VALUE OF ROUTINE SKULL X-RAYS

BY

JOHN BURKINSHAW

From St. James's Hospital, London

(RECEIVED FOR PUBLICATION JULY 14, 1959)

A blow on the head, especially if followed by symptoms of concussion, causes anxiety which is born of the knowledge that injury to the brain and other serious complications may occur. A child who attends hospital on account of a head injury is usually admitted for observation for signs of these complications and it is a common practice to x-ray his skull in order to find out whether it has been fractured. The primary object of the present investigation was to determine whether a routine skull x-ray of a child with a recent head injury gives information which helps the doctor either to give a prognosis or to decide on the treatment of his patient. The additional objects of the survey were to assemble information about the age, sex incidence, and causes of head injuries in children.

With these objects in mind I looked through the notes of all the children up to 13 years of age who had been admitted with head injuries into a general hospital in London during the years 1951 to 1956 inclusive. The relevant information was collected from the notes and has been analysed and tabulated. The parents of each patient were then sent a letter requesting their help and were invited to supply the answers to questions relating to the history of the child after discharge from hospital. The answers were scrutinized and the information so provided has been analysed and tabulated.

Criteria

A case was included in the survey if there was a history of a blow on the head and the child showed either some external evidence of the injury (laceration, haematoma or abrasion) or had had symptoms suggesting concussion (disturbance of consciousness or memory, drowsiness). Cases were not included where it was clear from the history and appearance of the wound that the injury was merely a simple incised wound and there were no symptoms of

concussion. Wounds of the face and eyes only with no symptoms of concussion were also excluded. Some patients had other injuries in addition to the head injury but they were not included unless the head injury satisfied the above criteria.

Classification

The cases were classified according to the severity of the concussion into the following three groups:

Group 1. Slight concussion. Injury to the head with no disturbance of consciousness or memory.

Group 2. Moderate concussion. Injury to the head with any of the following symptoms: Irritability, amnesia or drowsiness, with or without initial loss of consciousness or inaccessibility of less than one hour's duration or, loss of consciousness of less than one hour's duration without other symptoms.

Group 3. Severe concussion. Injury to the head with unconsciousness or inaccessibility for one hour or longer.

Owing to the lack of precise information in the notes about the accident it was necessary in a few instances to make a somewhat arbitrary decision as to the correct classification of the case, and this inevitable weakness of a retrospective survey from case notes must be borne in mind.

Criteria for Admission

Admission of cases to hospital depends upon the assessment of the admitting doctor. Over this period of six years when many different doctors were concerned, each one with his own views and judgment, it is unlikely that there has been true

uniformity of the criteria for admission into the hospital. Furthermore, it is possible that in London some cases of head injury may have been admitted to other hospitals. This would be most likely in the case of very severe injuries obviously in need of neurosurgical treatment. Such cases cannot be dealt with at St. James's Hospital and would very probably be admitted direct to a neurosurgical unit. For these reasons, therefore, the series under review cannot be taken to represent the whole picture of children with head injuries in this part of London and must be regarded merely as a series of 238 children with head injuries who were considered suitable for admission to a general hospital. The facts disclosed by this survey must therefore be interpreted accordingly. The series consists of 238 children, 182 boys and 56 girls. This gives a ratio of 3.25 boys to 1 girl.

Age and Sex Incidence

The figure shows the incidence by age and sex. The maximum incidence for both sexes is between the ages of 8 and 9 years (26 boys and eight girls) with secondary peaks in boys at 12 to 13 years (25 cases) and 4 to 5 years (15 cases) and in girls at 5 to 6 (6 cases) and 11 to 12 (7 cases). Table 1 shows the causes of the head injuries in numerical order of frequency in the boys and girls. The ratio of boys to girls injured by each cause is also shown.

Traffic Accidents (60 boys : 18 girls). These include collision with road vehicles of all kinds, including bicycles and cases where the child was in a vehicle which was involved in an accident. They do not include falls from vehicles—notably bicycles when the bicycle or other vehicle itself was

TABLE 1

Cause of Head Injury	Boys	Girls	Ratio	
			Boys	Girls
Traffic accidents	60	18	3.3	1
Miscellaneous falls	42	19	2.2	1
Fall from height	29	7	4.1	1
Fall off bicycle	20	2	10	1
Hit by moving object	10	3	3.3	1
Fall off moving vehicle	10	0	10	0
Fall down stairs	5	2	2.5	1
Fall off swing	1	3	0.3	1
Fall out of bed	2	0	2	0
Fall in bus	0	1	0	1
Assault	0	1	0	1
Cause uncertain	3	0	3.0	0
Overall ratio { Boys 3.25 Girls 1.0	Total 182	56	3.25	1

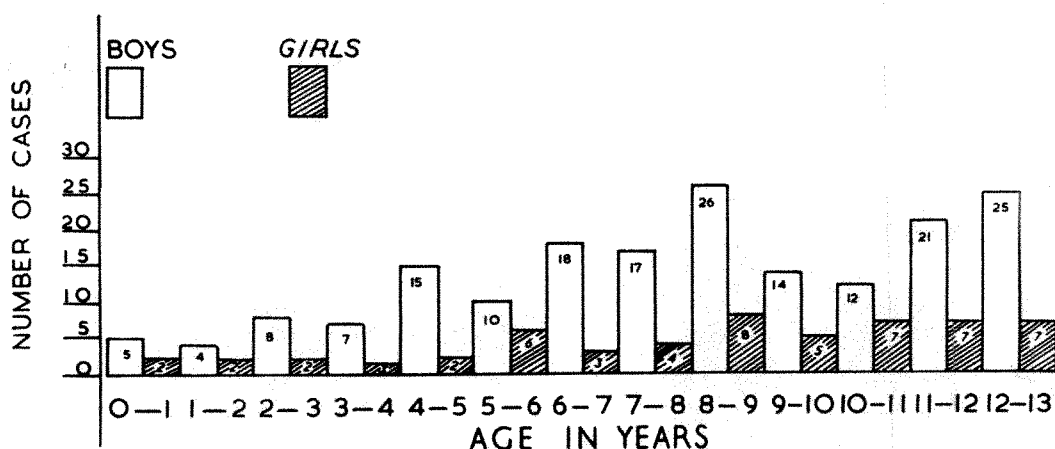
not involved in a collision. Thus if a boy simply falls off his bicycle the injury is classified as 'fall from bicycle' but if he runs into another bicycle or a car it is a 'traffic accident'.

Miscellaneous Falls (42 boys : 19 girls). These include all falls when the child was on the ground or, in the case of a few infants, was being carried and the carrier either fell herself or dropped him. Most of these occurred while at play, and frequently occurred in the school playground.

Falls from Height (29 boys : 7 girls). These include injuries when the child fell to the ground from something above the ground—e.g. out of windows, off walls, trees, tables or ladders.

Falls off Bicycle (20 boys : 2 girls). These falls were much commoner in boys.

Hit by Moving Object (10 boys : 3 girls). This category includes all injuries caused by impact with a moving object other than a vehicle, such as



Age and sex incidence.

TABLE 2
CASES CLASSIFIED ACCORDING TO SEVERITY SHOWING PRESENCE OR ABSENCE OF FRACTURE

	Total Cases	Total	No Fracture % of X-rayed Cases	Total	Fracture Present % of X-rayed Cases	Total X-rayed	Not X-rayed
Severe	17	8	50	8	50	16	1
Moderate	135	96	80	23	20	119	16
Slight	86	52	78	15	22	67	19
Total cases	238	156		46		202	36

stones, bricks, falling ladders. The other causes listed in the table do not need further explanation or comment.

Fracture of the Skull in Relation to Severity of Concussion

In Table 2 the cases have been arranged to show the numerical relation between the severity of the concussion and the presence or absence of a fracture of the skull. It will be seen that out of x-rayed cases with severe injury 50% had a fracture of the skull; of x-rayed moderately concussed cases 20% had a fracture; and of those with slight concussion 22% had fractures. A proportion of cases in each category did not have an x-ray of their skull, so that they cannot be included in this particular analysis.

Site of Injury. Table 3 shows the site of the injury to the head in order of frequency and occurrence. It will be seen that right-sided injuries are commoner than left but that the majority of injuries involve the midline and both sides of the head adjacent thereto.

Cases with Complications. When localizing signs were present at the time of the initial clinical assessment, or if the patient's condition deteriorated,

TABLE 3
SITE OF INJURY

	Right	Left	Midline with involvement of both sides	Total
Frontal	23	13	28	64
Occipital	3	4	21	28
Parietal	18	7	2	27
No external signs of injury				26
Facial	4	2	17	23
Uncertain				21
Temporal	8	11	0	19
Injuries at two sites				13
Injury at one site; fracture at another				11
Bleeding from nose only	2	1	0	3
Bleeding from ear only	2	1	0	3
	60	39	68	238

or some new symptom or sign made its appearance, the case was considered to have been attended by a complication. Thus, for instance, if some hours after the injury a patient who was conscious, complained of a headache and had hitherto not done so, the headache was regarded as a complication of the injury. If, on the other hand, the patient had complained of a headache as soon after the injury as he was able to express himself, that would not be classed as a complication.

Table 4 shows the cases with complications as

TABLE 4
CASES WITH COMPLICATIONS SHOWING SEVERITY, PRESENCE OF FRACTURE AND SEQUELAE

Case No.	Severity	Fracture	Nature of Complications	Sequelae	Nature of Sequelae
22	Severe	+	Unconscious 18 days; blindness; dementia	+	Dementia; blindness
33	Moderate	+	Meningitis	+	Headaches frequent→occasional
73	Slight	○	Headache	+	Occasional headache
76	Moderate	+	Headache	+	Occasional headache
91	Severe	+	Subarachnoid haemorrhage	○	
96	Slight	○	Headache	+	Occasional headache
99	Slight	○	Headache; vomiting	○	
102	Moderate	○	Diplopia for 5 days	+	?
124	Moderate	○	Headache; depression	*NR	Nerves; occasional headache
140	Severe	+	Lt. hemiparesis; 2 major fits; giddy spells; ocular palsy; attended special school for 10 months	*NR	(Last seen 10 months after injury; well; no fits; no paresis)
142	Severe	+	Died	—	
154	Moderate	○	Headache	†NT	
193	Moderate	○	Headache	○	
207	Severe	○	Weakness of rt. arm 2 weeks	+	School work worse
215	Moderate	○	Headache	+	Aggressive; headaches frequent→occasional
217	Slight	+	Large occipital subaponeurotic haematoma	○	
235	Moderate	+	Rt. facial weakness 3 weeks	+	Headaches frequent→occasional

* NR = No reply.

† NT = Not traced.

defined above. The severity of the concussion and the presence or absence of a fracture of the skull are shown in each case.

Table 4a shows the relationship between the

TABLE 4A
CASES WITH COMPLICATIONS ACCORDING TO SEVERITY
AND PRESENCE OF FRACTURE

Severity	Number	% of Total in Each Category	With Fracture	No Fracture
Severe	5	29	4	1
Moderate	8	5	3	5
Slight	4	4	2	2
Totals	17		9 (19%)	8 (5%)

severity of the concussion and the presence or absence of a fracture in these cases with complications. It will be seen that nearly half (8/17) of these patients had no fracture of the skull and that just over half (9/17) did have a fracture. The figures in brackets show the percentage of cases in the three categories of severity which were attended by complications. Of severe injuries 29% were followed by complications; the rate with moderate injuries was 5% and with slight injuries 4%. Table 4a also shows the number of cases in each grade of severity in which a fracture was found. Four out of five severe cases with complication had a fracture; three out of eight moderate cases had a fracture and two out of four of the slight cases had a fracture.

Follow-up

Further information is available about 135 of the original 238 cases. This number includes the one

patient who died shortly after the injury (Case 142) and the one with dementia and amaurosis (Case 22), who is in a home. Information about the remaining 133 cases is derived from answers to a questionnaire which was sent to the mothers of all the patients in the original series. The minimum period between the original injury and the date of the reply was one whole year and the maximum period was six whole years.

Sequelae. The symptoms and untoward effects under consideration were regarded as sequelae if they occurred after return home from hospital and they had not been present before the injury occurred.

Tables 5 and 6 show the incidence of various sequelae about which information was specifically sought. In Table 5 the cases are grouped according to the presence or absence of a fracture of the skull, and in Table 6 the grouping is according to the severity of the concussion. It will be seen from these two tables that of cases with fractures 66% had sequelae and of those with no fracture 49.5% had sequelae. Of cases classed as severe (including the one who died), 61.5% had sequelae; of cases classed as 'moderate', 51.5% had sequelae and of cases classed as 'slight' 52% had sequelae.

With the single exception of the one child who is permanently demented and blind, there is no surviving child in the follow-up series who is suffering from sequelae which would be noticeable to anyone who did not know the child before the accident, and the majority of symptoms complained of in the answers might readily be explained away as coming within the range of normality.

TABLE 5
CASES WITH SEQUELAE ARRANGED ACCORDING TO PRESENCE OR ABSENCE OF FRACTURE (PERCENTAGES TO NEAREST ½%)

Nature of Sequela	Fracture +	% of Total Cases with Fracture	No Fracture	% of Total Cases without Fracture	Not X-rayed	% of Total Cases not X-rayed	Total Cases
Fits	0	0	1	<1	0	0	1
Personality change	8	29.5	19	21	3	17.5	30
Better	0	0	10	11	1	6	11
School work							
Worse	3	11	10	11	2	12	15
Ataxia, etc.	1	3	2	2	0	0	3
Blindness	1	3	0	0	0	0	1
Occasional	5	18	14	15.5	4	24	23
Headaches							
Frequent	4	15	3	3	2	12	9
Frequent→occasional	4	15	5	5.5	1	6	10
Died	1	3	0	0	0	0	1
Compensation paid	2	7.5	6	6.5	2	12	10
No sequelae	9	33	46	50.5	9	53	64
With sequelae	17	66	45	49.5	8	47	70
Total cases	27		91		17		

TABLE 6

CASES WITH SEQUELAE ARRANGED ACCORDING TO SEVERITY OF CONCUSSION (PERCENTAGES TO NEAREST ½%)

Nature of Sequela	Slight Injury	% of Total Cases with Slight Injury	Moderate Injury	% of Total Cases with Moderate Injury	Severe Injury	% of Total Cases with Severe Injury	Total Cases
Fits	0	0	1	< 1	0	0	1
Personality change	13	25	13	18.5	4	30	30
Better	6	11	4	6	1	7.5	11
Worse	3	5.5	7	10	5	38	15
Ataxia, etc.	1	2	1	2	1	7.5	3
Blindness	0	0	0	0	1	7.5	1
Occasional	7	13	15	21	1	7.5	23
Headaches							
Frequent	4	7.5	3	4	2	15	9
Frequent→Occasional	3	5.5	7	10	0	0	10
Died	0	0	0	0	1	7.5	1
Compensation paid	7	13	2	3	1	7.5	10
No sequelae	25	48	34	48.5	5	38	64
With sequelae	27	52	36	51.5	7	54	70
Total cases	52		70		13		

Fits. Personality changes were reported in 30 (22%) of the cases in the follow-up series. Table 7

TABLE 7
THE 30 CASES WITH CHANGE OF PERSONALITY

Description	No.
Nervous or highly strung	14
Outbursts of anger and bad temper	6
Sleep difficulties	4
'Phobias' (ladders; heights)	2
Depression	2
Faints	1
'More careful now'	1
Nervous stomach aches	1
Laziness	1
Stuttering	1
Aggressive	1

shows the changes of personality described by those who replied to the questionnaire. In none of the above cases was the change of personality very pronounced and it is, of course, impossible to say whether the change was the result of the injury or of other causes. The only evidence that the injury contributed to these changes is that, according to the parents, they made their appearance shortly after the injuries had been sustained.

School Work. In 11 cases (8%) the parents reported an improvement in school work dating from the return to school after the injury. In 15 (11%) there was a deterioration. The only case who could not receive normal education was Case 22 who is in an institution for mentally defective children and who is also blind as a result of the accident. The parents of some children could not judge the change in intellectual status because they were too young at the time of the accident to attend school. In all cases the change in school work was

not very great and in all there was a steady improvement up to the time of the receipt of the questionnaire, the majority of cases having completely regained their previous status.

Ataxia. Parents were questioned specifically about muscular paralysis or weakness and none of the parents who replied to the questions would admit to muscular paralysis in their children, but one child was stated to have lost her sense of balance, one was stated to be more clumsy after the accident, and one to have 'weakness' with no further amplification of the term. The blind child (Case 22) had cortical blindness.

Headaches. Forty-two children (31%) of the follow-up series were reported as having had headaches which dated from the head injury. They have been grouped according to whether the headaches were stated by the parents to be 'frequent' or 'occasional'. No great reliance must be placed upon this classification because no definition of these terms was suggested to the parents, so that the numbers included under these headings are not properly comparable. A third heading is assigned to cases whose headaches were stated to have been frequent at first but which had become only occasional by the time the questionnaire was received. As with the school work and personality change none of these children was seriously handicapped by the headaches, and it is easy to argue that they might well be no more frequent or severe than the headaches felt by any child from time to time.

Compensation. The parents had been asked whether compensation for the injury had been sought

TABLE 8
CASES IN WHOM COMPENSATION WAS PAID

Case No.	Cause of Injury	Severity	Skull Fracture	Other Injuries	Sequelae
36	Fell off swing	Moderate	○	○	Headaches frequent
71	Traffic accident	Slight	○	Leg injury	Nerves; insomnia
82	Traffic accident	Moderate	○	○	Photophobia; nerves; temper; sleep difficulty; headaches
87	Fell off bus	Slight	○	○	○
95	Traffic accident	Slight	+	Abrasions	Nerves; afraid of heights; school work worse
106	Traffic accident	Slight	○ ×	Abrasions	Nerves; frequent headaches
121	Hit by ladder	Slight	+	○	Frequent headaches
165	Traffic accident	Slight	○ ×	Abrasions	○
207	Traffic accident	Severe	○	Abrasions	School work worse
221	Traffic accident	Slight	○	Leg	Occasional headaches

○ × = Not x-rayed.

or received. The object of this was to provide evidence about the frequency of litigation in these cases and also to determine what relation existed between the litigation and the incidence of sequelae. In 10 (7.4%) cases compensation had been paid. Information about these cases is set out in Table 8. In seven out of the 10 patients receiving compensation the head injury had been assessed as 'slight', for two the assessment was 'moderate' and one 'severe'. In six cases there was no fracture of the skull, in two a fracture was present and one was not x-rayed. In one case the compensation was admitted by the parents to have been paid on account of a leg injury sustained at the same time. In seven of the compensated cases the injury was sustained in a traffic accident, one fell off a swing in a public playground, one fell off a moving bus, and one was hit by a falling builder's ladder.

Depressed Fracture. Table 9 shows the four cases in which a diagnosis of depressed fracture was made, either clinically or radiologically. In one case a depressed fracture was missed clinically, and in one it was suspected clinically but not confirmed radiologically. In one case, in spite of the assessment of the injury as 'slight', the patient's depressed fracture was surgically elevated, and the patient had no complication or sequelae. In the patient whose injury was compound and obviously very severe, brain toilet was carried out but the patient died without recovering consciousness. In the remaining

two, treatment was conservative, and of these two patients one had 'frequent-becoming-occasional' headaches as a sequela.

Discussion

Sex Incidence. That boys injure their heads more often than girls is a fact which will not surprise those who are familiar with the ways of children. 'Boys will be boys' is a proverbial truth which must be remembered when planning a programme of investigation into the causes of accidents in children or when preparing any scheme for preventing their occurrence. The restless exploration and aggressiveness of the male are biologically useful to the species in many obvious ways and the tendency of boys to behave as if they were expendable is to the more sedate and careful behaviour of girls, as the reckless mobility of the spermatozoon is to the more sedentary and egocentric habits of the ovum.

Age Incidence. The two age peaks of head injuries shown in the figure provide scope for speculation as to their significance. They are capable of being interpreted as reflecting, in the first peak a phase of development when the child's co-ordination is unequal to his demands upon it, and in the later peak, the intense preoccupation with his activities which makes a boy so heedless of danger.

Cause of Injury. As might be expected traffic accidents accounted for about 33% of the injuries

TABLE 9
CASES WITH DEPRESSED FRACTURE

Case No.	Site of Fracture	Diagnosis		Severity	Treatment	Complications	Sequelae
		Clinical	X-ray				
76	Rt. frontal	○	+	Moderate	Nil	Headache	Occasional headache
92	Rt. parietal	+	+	Slight	Elevation	○	○
102	Lt. frontal	?	○	Slight	Nil	○	○
142	Rt. temporal	+	+	Severe	Brain toilet	Died	—

to both sexes. The only cause which affected girls more often than boys was 'falls off swing', 'fall in bus' and 'assault'. It is perhaps important to know that boys are more liable to be injured by most of the listed causes and not only by traffic accidents, because the chances of a boy being partly responsible for his injury in a traffic accident would appear to be greater than is the case with a girl.

Other Aetiological Factors. Because of lack of the necessary data in the notes it was not possible to go into several other possible aetiological factors which might have been interesting. Among these are the time of the day, the month of the year, the state of the weather, the number in the family, the economic status of the family, the psychological set-up in the home and the emotional or physical state of the child at the time. In planning a future investigation these things might profitably be taken into account.

The Value of Diagnosing a Fractured Skull. The primary object of this investigation was to assess the value, if any, of x-raying the skull in children with head injuries. An x-ray of the skull might possibly be of value if it provided affirmative answers to three questions: (1) Does the finding of a fracture of the skull in the x-ray make necessary any change in the treatment of the case? (2) Does the finding of a fracture of the skull in the x-ray afford more reliable guidance than clinical assessment alone as to the probability of complications? (3) Does the finding of a fracture of the skull in the x-ray afford more reliable guidance than clinical assessment alone as to the probability of sequelae?

With regard to Question 1 relating to immediate treatment, all the cases in this series had been admitted to hospital on account of injuries and all were kept at rest and under close observation. This line of treatment is generally accepted as correct for all cases of head injury and no one would dispute the wisdom of it. If it could be shown that the absence of a fracture of the skull made admission unnecessary, that in itself would fully justify the taking of an x-ray. That such criterion for admission is invalid is shown by Table 4 where it will be seen that of the 17 cases who developed complications nine had a fracture and eight had none.

The Closed Depressed Fracture. Apart from rest and close observation and symptomatic treatment all but two of the cases had no other treatment. The two who were treated surgically both had depressed fractures. One (Case No. 142)

was very severely injured and died after brain toilet in another hospital. The gross and obvious damage to the skull was the indication for this treatment rather than the finding of a depressed fracture, an x-ray finding which merely supported the clinical decision to operate. The second case (No. 92) of depressed fracture had his fracture elevated in accordance with surgical tradition. As has already been pointed out, this child's injury according to the criteria adopted in this investigation was classified as 'slight'. This boy had no untoward symptoms at the time or afterwards. On the other hand one of the four cases with depressed fracture (No. 26) had no surgical treatment and still does complain of occasional headaches. This child's fracture had not been diagnosed clinically. Might he have been saved from these headaches if his depressed fracture had been elevated? If the answer to that question is in the affirmative there can be said to be a case for x-raying all skulls in order to detect missed depressed fractures.

In one case (No. 120) a depressed fracture had been suspected clinically but was not confirmed radiologically. The information about depressed fractures to be had from this investigation is insufficient to justify any conclusion and the writer's experience of the management of such cases is also too meagre for him to venture an opinion. There is wide agreement among leading authorities that operation is advisable for closed depressed fractures of severe degree but for depressed fractures of lesser extent, just the kind that might most easily be missed without an x-ray, a number of authors advise conservative treatment. Dickson Wright and Handfield-Jones (1957) write: 'Simple depressed fractures in children should not be operated upon at first because a great many recover spontaneously. If later elevation of the fragment is deemed necessary all bruising of the soft tissues will have subsided and the danger of infection is thereby lessened'. Browder (1949) writes: 'Instances in which the extent of the depression of the inner table is estimated to be only a few millimetres require only conservative measures unless there is evidence of intracranial complication'. Aird (1957) writes: 'Certain depressed fractures require operation. Most depressed fractures in adults are compound and require operation for that reason; pond fractures in children do not *per se* require operation'.

Wakeley (1952) states: 'In closed depressed fractures in adults always operate; in children if gutter shaped operate; if pond shaped wait for symptoms unless the fracture is a bad one'.

Rowbotham (1949) gives four indications for operating on a closed depressed fracture. (1) When

a patient is unconscious and thought to be suffering from cerebral compression. (2) When there are signs of underlying brain damage. (3) When a fragment of bone is thought to have penetrated the dura. (4) Cosmetic considerations. *Christopher's Textbook of Surgery* (1956) states, 'the majority of patients with simple depressions should be operated on except those having slight depression in the frontal area and small simple depression in the midline and the large venous sinuses'. Bailey and Love (1956) state, 'treatment depends on the extent of the depression and the site of the injury'.

After considering the views expressed by the authorities quoted above one must concede that where there is a clinical suspicion that a depressed fracture may exist it is advisable to x-ray the skull in order to settle the matter. But in a large number of cases which are being discussed the clinical findings were such that even if a depressed fracture were present it would only be a slight 'pond' fracture, of the type that would merely require conservative treatment. It does not seem, therefore, to be necessary to x-ray the skull immediately merely to detect a slight depressed fracture. It should be quite safe to confine x-rays to those cases where there was clinical suspicion of a depression or where surgical intervention was clearly indicated on account of a deterioration in the patient's condition.

The Non-Depressed Fracture. After leaving the troubled waters of the depressed fracture question, one encounters much plainer sailing, and it is beyond dispute that treatment of children with head injuries is exactly the same whether a fracture is demonstrated by the x-ray or not. The chief function of the skull is to protect the brain from damage and this it does remarkably well, though in absorbing the force of a blow, the bone often sustains a fracture. It is a matter of physics that the harder the blow the greater will be the chance of a fracture, but Table 2 shows that, whereas, among severe cases, as defined in this paper, there is a 50/50 chance of the skull having been fractured, the chance of a fracture in cases of moderate or slight severity is approximately the same, namely around 20%.

Question 2 relating to the likelihood of complications can be answered by study of Tables 4 and 4a. These tables show that of the 17 cases which were attended by complications five were severe, eight were moderate and four were slight. Nine had fractures and eight had no fracture and in none of these cases was an x-ray of the skull omitted. Table 4a shows that 29% of severe cases and less

than 10% of the moderate and the slight cases were attended by complications. This table also shows that 19.5% of cases with fractures and 5% of those without fractures were attended by complications. If the incidence of complications in the severe cases is compared with the incidence of complications in the combined slight and moderate cases, the percentages are found to be 29% and 5% respectively. The occurrence of complications can be substantially as accurately forecast, therefore, if judged according to the clinical assessment as according to the presence or absence of a fracture.

The conclusion with regard to Question 2, therefore, is that a skull x-ray is a no better means of foretelling the occurrence of complications to head injury than the clinical assessment of the case alone.

With regard to Question 3, if the cases with sequelae are arranged according to whether a fracture was present or absent, as in Table 5, and then according to severity as in Table 6, a comparison between the two tables will throw some light on the prognostic value of the two methods of classification in regard to the incidence of sequelae.

The three sequelae which occurred in sufficient numbers to merit comparison, are 'Personality Change', 'Changes in School Work' and 'Headaches'. These sequelae were all slight and did not really cause any material disability. Indeed in most cases it would be hard to refute the allegation that the sequelae reported by the parents were in fact quite unrelated to the head injury and were chance occurrences such as might befall any child. It is important to bear in mind that the writer is not attempting to convey the impression that the figures quoted are an accurate numerical account of the incidence of sequelae of head injury. To do this would require a proper control series consisting of children of similar ages who had been in hospital for similar periods of time on account of some disease such as appendicitis. Nevertheless the cases can be used as their own controls to test the relative merits of classification by x-ray and by severity as a means of assessing the likelihood of occurrence of sequelae.

Personality Change. When the cases are arranged according to the presence or absence of a fracture, Table 6 shows that a personality change occurred in 29.5% of cases with fractures and in 21% of cases with no fracture. When classified according to severity, the results are as follows: Severe 30%, moderate 18.5% and slight 25%. If slight and moderate cases are combined, the percentages are: Severe 30%, slight or moderate 21%.

School Work. It was surprising to receive so many replies to the effect that school work had, in the opinion of the parent, actually improved after the injury, but this must be accepted with considerable reserve as to its significance and certainly should not be construed as a possible line of treatment for the mentally sluggish. If the cases showing an improvement are arranged in the same way as was done for cases with a change in personality the results are as follows:

Fracture present ..	0.0%	
No fracture ..	11.0%	
Severe ..	7.5%	
Moderate ..	6.0%	} Combined 8%
Slight ..	11.0%	

A greater incidence in the slightly injured cases is what might be expected.

The corresponding figures for cases where school work deteriorated are:

Fracture present ..	11.0%	
No fracture ..	11.0%	
Severe ..	38.0%	
Moderate ..	10.0%	} Combined 8%
Slight ..	5.5%	

Headaches. With regard to headaches the figures are as follows:

(a) *Occasional headache*

Fracture present ..	18.0%	
No fracture ..	15.5%	
Severe ..	7.5%	
Moderate ..	21.0%	} Combined 18%
Slight ..	13.0%	

(b) *Frequent headache*

Fracture present ..	15.0%	
No fracture ..	3.0%	
Severe ..	15.0%	
Moderate ..	4.0%	} Combined 5%
Slight ..	7.5%	

(c) *Frequent headaches becoming occasional*

Fracture present ..	15.0%	
No fracture ..	5.5%	
Severe ..	0.0%	
Moderate ..	10.0%	} Combined 8%
Slight ..	5.5%	

The figures as set out above show that with the possible exception of 'occasional headaches' the incidence sequelae of these cases is as well correlated with the severity of the injury as with the presence or absence of a fracture. It is therefore possible to conclude that an x-ray of the skull is no more reliable as a guide to assessing the likelihood of sequelae than the clinical assessment of the case alone.

Conclusion

The facts and figures here presented, though perhaps not statistically conclusive, suggest that apart from the possibility of diagnosing a depressed fracture the routine taking of a skull x-ray in cases of children with head injury serves no useful purpose. It does not help the doctor in his immediate treatment of the case and it is no more reliable than clinical assessment alone as a guide to the likelihood of complications or of sequelae. When a limb bone is fractured the most important consideration is the restoration of the limb's function, which is movement. The limb bones serve as an attachment for the muscles and provide the levers whereby movement of the limb is brought about. When a limb bone is broken abnormal movement may occur at the point of fracture and, if the fragments of the broken bone are not properly aligned, there may be a permanent impairment of the efficiency of the limb. It is therefore important when limb bones are fractured to use x-rays in order to help to bring about as perfect a realignment of the bones as possible. The skull bones, however, are not mainly concerned with the function of movement, and they are so arranged that they are very well splinted by each other and by the overlying aponeuroses and other structures. Their outstanding function is that of a protective armour and as such are designed to be bent and battered to a considerable degree without losing their protective function. There is, therefore, no clinical need to know in every case the precise extent to which the bones have been broken and battered and it is this difference coupled with the knowledge suggested by this investigation which justifies the doctor in omitting to take a routine x-ray of the skull after a head injury and to reserve this investigation for cases for whom it is considered on clinical grounds to be necessary.

The indications for an immediate skull x-ray in children with head injuries appear to be as follows:

- (1) In order to obtain evidence that the head has been struck in cases where the suspicion exists but where no external signs of damage to the head can be found.
- (2) In order to confirm a clinical suspicion of depressed fracture.
- (3) In order to define the extent of damage to the bones in cases where immediate surgical treatment is contemplated.

Many doctors continue, as a routine, to x-ray the skulls of their patients with head injuries although they are by no means convinced of the value of doing so. If asked why they do so they will reply that they do it to provide themselves with 'medico-

legal cover'. Lawyers do not know much about medical practice but they rightly expect a doctor to have acted in accordance with accepted medical practice. If, therefore, doctors always take skull x-rays merely to satisfy the lawyers, one can hardly blame the lawyers for expecting them to continue to do so. It is the doctors' duty to teach the lawyers that when treating a child with a head injury an x-ray of the skull is not always an essential item in the correct management of the case. It is only after they have been taught this lesson that the lawyers will cease to expect a skull x-ray on all occasions.

I wish to thank Mr. Metcalfe and Mr. Thomas for

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THE IMPORTANCE OF ACCIDENT-PRONENESS IN THE AETIOLOGY OF HEAD INJURIES IN CHILDHOOD*

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The term 'accident-proneness' was originally coined by Farmer and Chambers (1926) to describe a concept arising out of the observations of Greenwood and Woods (1919) and Newbold (1926). These workers had studied the distribution of accidents among factory hands and found that a relatively large proportion of accidents was reported from a relatively small proportion of the population at risk. This undue concentration of accidents could not be explained by chance variations or variations in exposure to danger. It was concluded that certain individuals had some sort of personality trait which rendered them more liable to have accidents. This trait (accident-proneness) seemed to be independent of the environment and constant for the individual from year to year.

Accident-proneness is now also used to denote a somewhat similar concept which has arisen from the psychological study of particular case-histories. Groddeck (1923), Menninger (1936) and others have suggested that many accidents are not entirely fortuitous but are in some way caused by the injured persons themselves. The process is said to be unconscious and motivated by complex desires for self-punishment and death. Flanders Dunbar (1943, 1947) attempted to combine both psychological and statistical approaches to the subject.

The existence of accident-proneness is now widely accepted. There is still, however, a considerable difference of opinion on its place in the aetiology of accidental injuries in general. Some workers (Heinrich, 1941; Dunbar, 1947) regard it of major importance but others (Adelstein, 1952; Schulzinger, 1954) think that it is of little significance. A common view, quoted by Schulzinger, is that 'the accident-prone 15% of the population causes 85% of the accidents'. Attempts to predict accident-

proneness have not met with much success (Chambers, 1955).

Little work has been done on accident-proneness in childhood. Ackerman and Chidester (1936) presented a case-history of a girl who had repeated accidents. Bakwin and Bakwin (1948) reviewed the subject. Some individual and social comparisons have been made between children who have had one or more accidents and those who have not. Differences have been found, but it is remarkable how small these are. For instance, 'accident-repeaters' have been found to be more aggressive, impulsive and rebellious (Birnbach, 1948), obstinate, impatient, vigorous, hyperactive, rude and highly-strung (Fuller, 1948), but the meaning of such differences is hard to assess. In children under the age of 5 years, Douglas and Blomfield (1958) found little difference in housing conditions, social class or maternal care between accident and control groups; children with two or more accidents were found to have slightly better physical development and mental ability. Langford, Gilder, Wilking, Genn and Sherrill (1953) found no neurological, ophthalmological or intellectual differences between a small group of accident-repeaters and controls. An increased number of accidental injuries has been reported in the families of injured children compared with the families of control groups (Langford *et al.*, 1953; Backett and Johnston, 1959). This has also been recorded in adults (Dunbar, 1943).

The present work was undertaken in an attempt to see whether accident-proneness plays a significant part in the aetiology of head injuries in childhood.

Material

Two series of observations were made. For the first series the case notes were examined of all children with head injuries admitted to Sheffield Children's Hospital between January 1, 1952 and December 31, 1958. Cases were included on the

* Based on a paper read to the Sheffield Regional Paediatric Society at Grimsby on June 6, 1959.

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following criteria: (1) The child's age was 13 years or under (but birth injuries were excluded). (2) The child was admitted to hospital because of the head injury or associated injuries. (3) There was a history of an accident which could have caused a head injury or obvious evidence of, for example, a fractured skull. (4) The child had one or more of the following: coma, stupor, drowsiness, confusion, vomiting, convulsions, lacerations of the head or bleeding from the nose or ear. These features were usually the reasons for the child's admission. Most of the children suffered mild or moderate head injuries, according to Symonds' (1949) classification. Seventeen children (11 boys and six girls) had severe injuries and three of these died.

The second series consisted of 30 patients with head injuries admitted to the same hospital between September 1, 1958 and April 30, 1959. These were seen personally and the parents interviewed. Full past and family histories were taken with special reference to accidental injuries, burns, and poisonings. These patients were matched by sex and age (to the year over the age of 2 years and to the quarter year below that), with 30 other patients admitted to the same wards during the same period of time. This control group was made up of acute medical cases, since closed head injuries are admitted to medical wards in this hospital. Eighteen of these children had acute infections (eight of the respiratory tract), three had rheumatic fever, two had anaphylactoid purpura, two chorea and five had other miscellaneous conditions. Similar histories were taken from the parents of these children. The two series overlap to some extent.

This hospital is a general children's hospital serving Sheffield and the surrounding districts. The great majority of the patients came from Sheffield itself.

First Series

Sex and Age. There were 1,180 cases of head injury in the first series of whom 825 were boys and 355 were girls. This is a ratio of 2.3 boys to one girl (Table 1). At all ages there were more boys with head injuries than girls. The number of boys and girls at each year of age in the general population of Sheffield is known from the census of 1951 (Registrar-General, 1951). Using these figures, it can be said that the excess of boys with head injuries is not significant ($\chi^2 = 2.75$; $n = 1$; $0.2 > p > 0.1$) under the age of a year. It becomes significant ($\chi^2 = 3.71$; $n = 1$; $p \approx 0.05$) for the first 2 years of life and highly significant ($\chi^2 = 6.63$; $n = 1$; $p = 0.01$) if the first 3 years of life are taken

TABLE 1
AGE AND SEX DISTRIBUTION OF THE CASES OF HEAD INJURY

Age in years	Boys	Girls	Totals	No. of boys per girl
Under 1	29	18	47	1.6
1-	51	34	85	1.5
2-	52	36	88	1.4
3-	62	38	100	1.6
4-	66	37	103	1.8
5-	69	34	103	2.0
6-	86	31	117	2.8
7-	86	30	116	2.8
8-	82	29	111	2.8
9-	82	21	103	3.9
10-	56	23	79	2.4
11-	42	8	50	5.3
12-	36	11	47	3.3
13-	26	5	31	5.2
	825	355	1,180	2.3

together. In general, after the age of 2 years, the ratio of boys to girls steadily increased with age.

The age and sex distribution of the cases are shown in Tables 1 and 2 and Fig. 1. It can be seen that the total number of cases rose steadily from the youngest age groups to a plateau at 6 to 8 years and thereafter declined. There were nearly four times as many cases at the age of 6, 7, or 8 years than at the age of 13 years.

There was a marked difference in the age distribution of head injuries in boys and girls. The peak frequency for girls was at the age of 3 years, followed by a steady decline with each older age group. The peak frequency for boys, on the other hand, was at the age of 6 to 9 years, and the numbers fell rapidly after that.

Month of the Year. Fig. 2 shows the monthly incidence of cases of head injury for each year of the survey. More cases regularly occurred in the summer than in the winter months. The whole series is summated for one year in Fig. 3, together with the distribution of cases according to sex and age group. Seasonal variations were most marked in the numbers of boys in the 0 to 4, and 5 to 9 year old groups.

TABLE 2
DISTRIBUTION OF CASES OF HEAD INJURY BY SEX AND AGE GROUPS

Age Group (years)	Boys	%	Girls	%	Totals	%	No. of Boys per Girl
0-4	260	22	164	14	423	36	1.6
5-9	405	34	145	13	550	47	2.8
10-13	160	14	47	3	207	17	3.4
	825	70	355	30	1,180	100	2.3

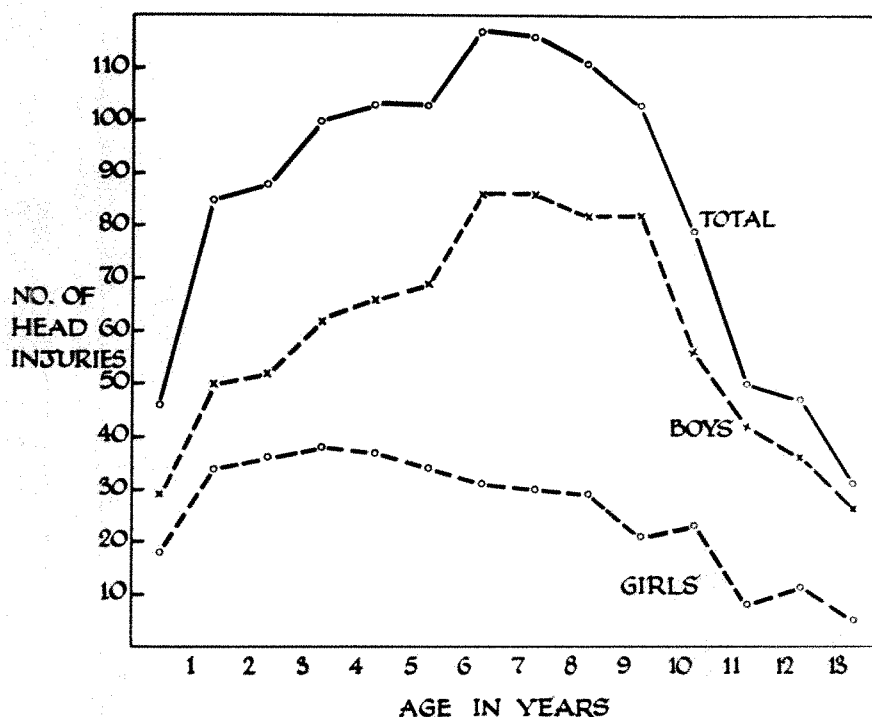


FIG. 1.—Age and sex distribution of all the cases of head injury from the first series.

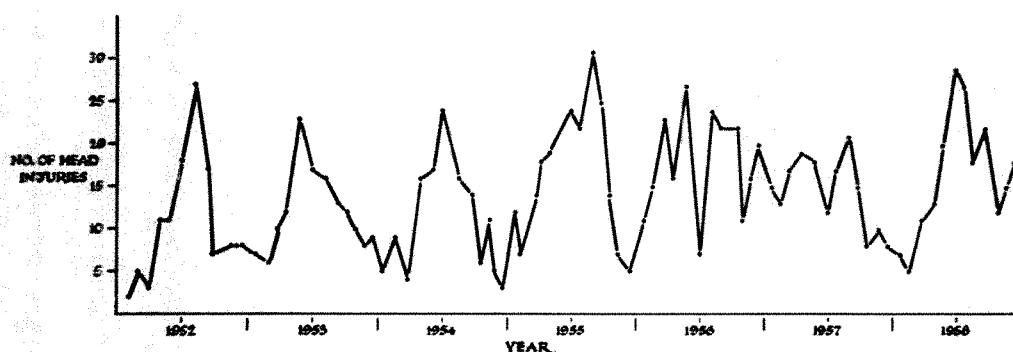


FIG. 2.—Monthly incidence of the first series of head injuries for each year of the survey.

Day of the Week. Fig. 4 shows the cases distributed according to the day of the week on which the accident occurred. There were only slight daily variations and the differences are not significant ($\chi^2 = 4.15$; $n = 6$; $0.7 > p > 0.5$). The ratio of boys to girls altered very little from day to day in the series as a whole and in the different age groups.

Time of Day. There was enough information in the notes to time the accident to the nearest hour in 649 cases (Fig. 5). There were two peak periods, one at midday and another larger one at 5 to 6 p.m. Each age group showed the same sort of pattern but it was least marked in the 10 to 13 year old group and most obvious in the 5 to 9 year old group.

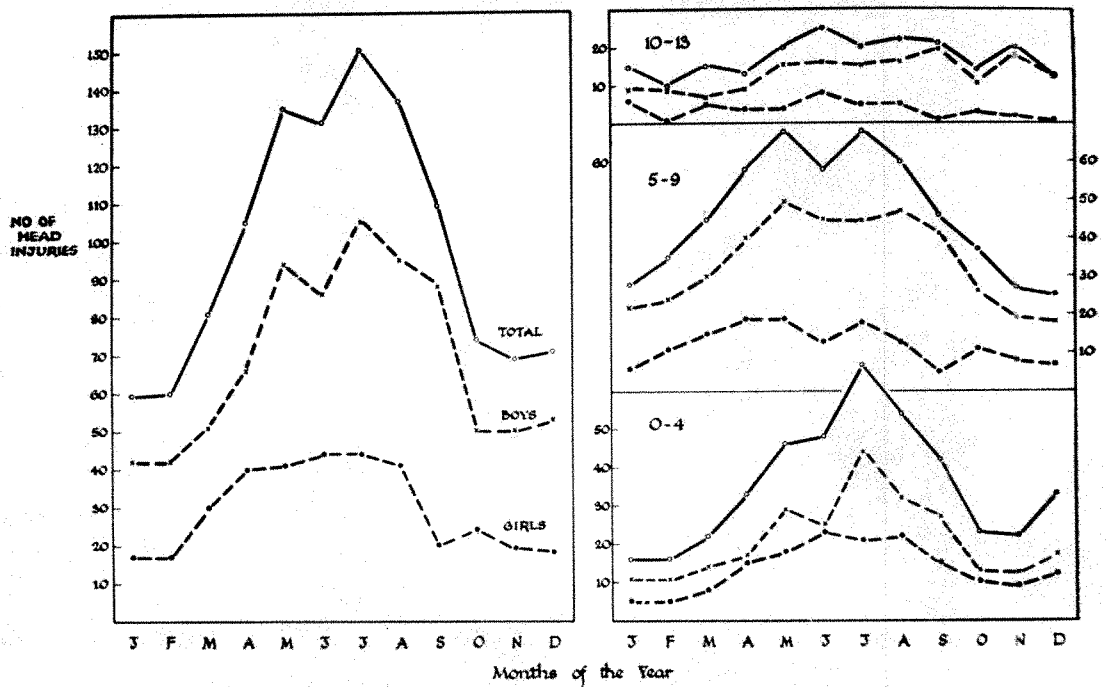


FIG. 3.—Distribution of the first series of head injuries by month of the year, sex and age-group.

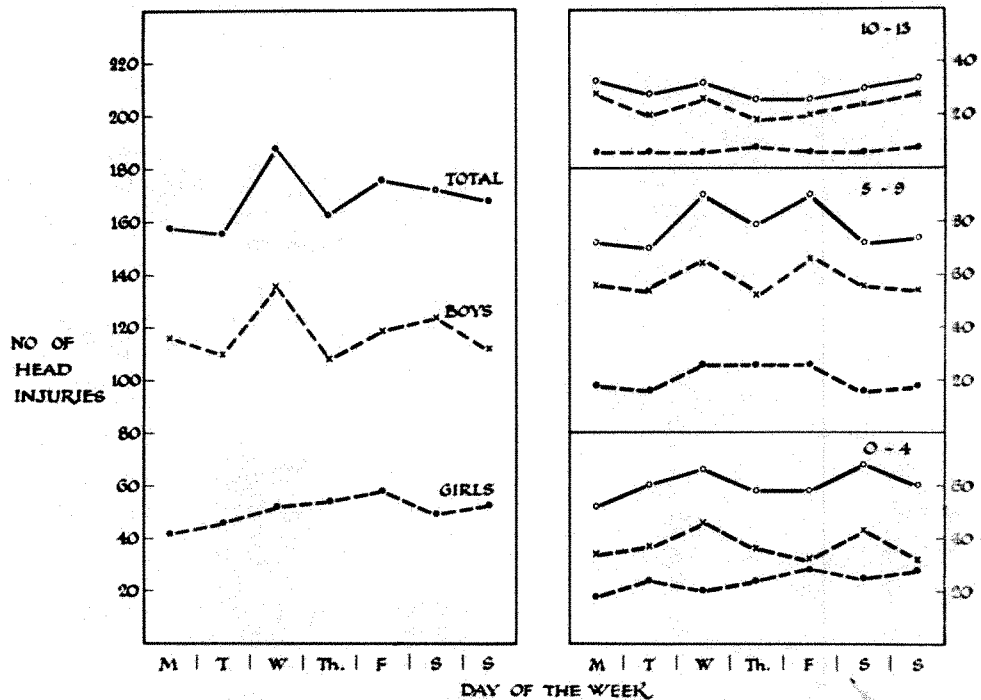


FIG. 4.—Distribution of the first series of head injuries by day of the week, sex and age-group.

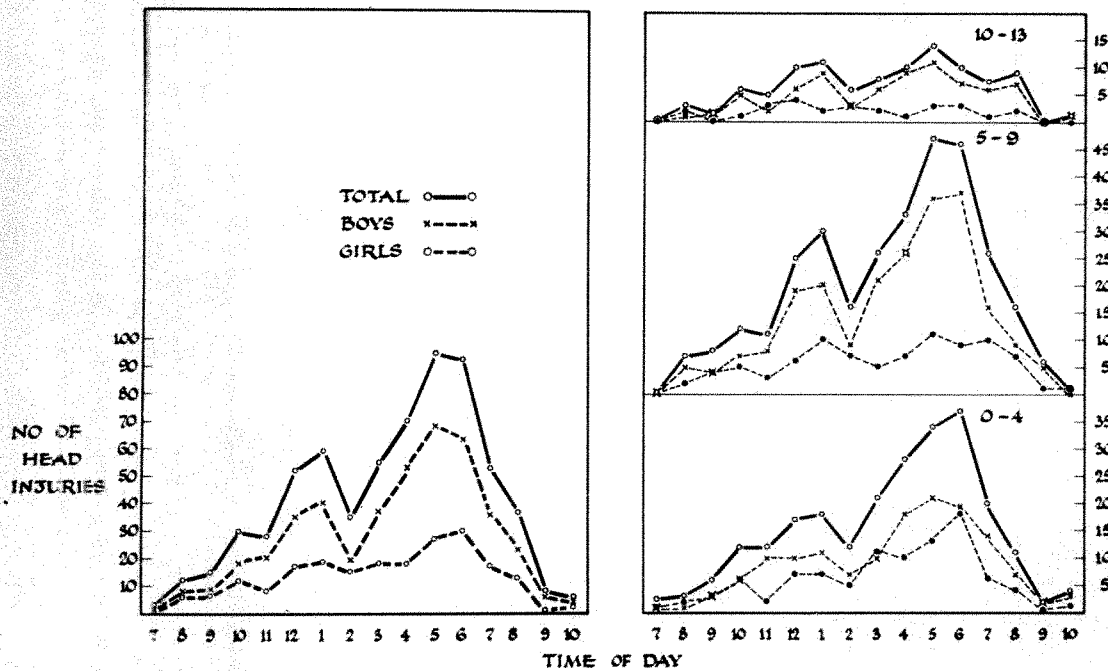


FIG. 5.—Distribution of 649 cases of head injury from the first series by time of day, sex and age-group.

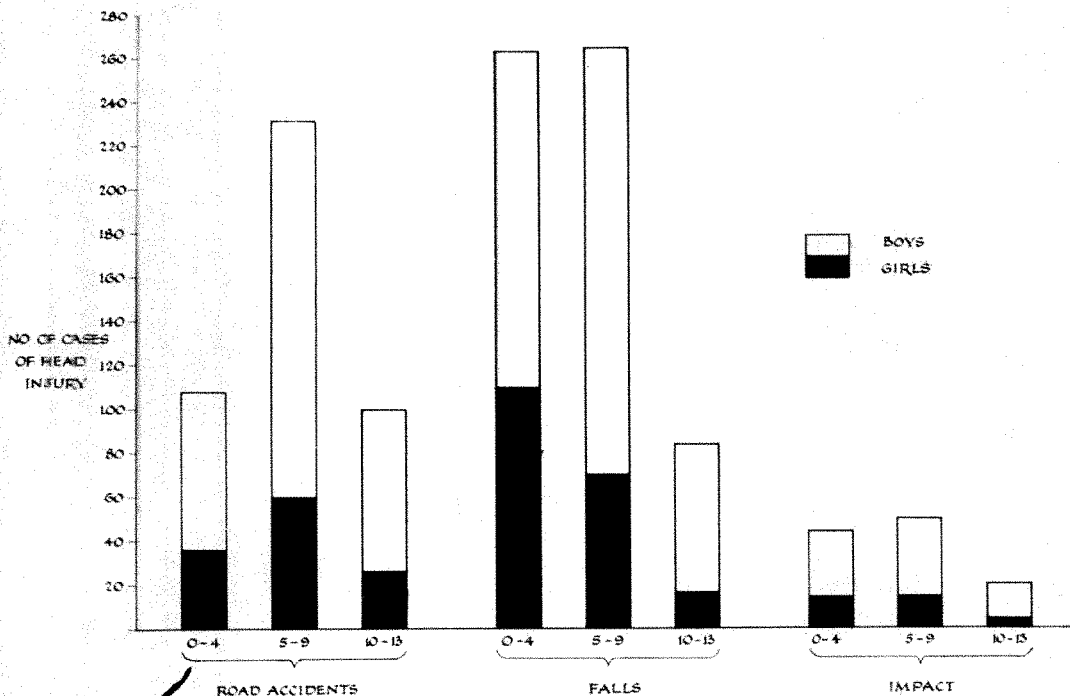


FIG. 6.—Distribution of 1,472 cases of head injury from the first series by type of accident, sex and age-group.

The peak frequencies in this latter group were almost entirely made up of boys, whereas the peak frequencies in the 0 to 4 year old group were made up of both boys and girls.

Type of Accident. Precise details of the accident causing the injury were seldom available. There was enough information, however, to classify the accidents into three main types. All accidents involving a moving vehicle were described as road accidents. Falls included falls from a height and falls on the child's own level. The term 'impact' was used for those cases in which the child was struck by or ran into an object. The results are shown in Fig. 6.

Falls were the largest category of accident. Falls were as common in the 0 to 4 year old group as in the 5 to 9 year old group. The 5 to 9 year old suffered more road accidents. There were more boys than girls in each age group of each type of accident.

Accident Repetition. The 1,180 cases were distributed among 1,155 patients. Nineteen children between them had 44 head injuries (Table 3). Put in another way, 1.6% of the children suffered 3.7% of the head injuries.

Fifteen of these accident-repeaters were boys and four were girls. This sex ratio is not significantly different ($\chi^2 = 0.37$; $n = 1$; $0.7 > p > 0.5$) from the rest of the series. At the time of their last injury, four were in the 0 to 4 year old group, 13 were in the 5 to 9 year old group and two were in the 10 to 13 year old group. None of these children sustained a severe injury. Thirty-two of the 44 accidents were falls, seven were road accidents and five were due to impact. This distribution is significantly different from the rest of the series ($\chi^2 = 7.42$; $n = 2$; $0.05 > p > 0.02$) and indicates that repeated head injuries were more often due to falls than to road accidents or impact.

In addition to these 19 children, 57 children had had one or more accidental injuries in the past

requiring medical attention (lacerations, known and suspected fractures, poisoning, etc.). In all, then, a total of 76 children (6.6%) had a past history of accidents at the time of their head injury. Sixty-three of these were boys and 13 were girls. This excess of boys is significant ($\chi^2 = 5.91$; $n = 1$; $0.02 > p > 0.01$) compared with the rest of the series. Sixty-five children had a past history of one accident, eight of two accidents and three of three accidents.

Second Series

The past and family history of children with head injuries was studied more closely for two reasons. In the first place it seemed likely that the past histories in the case notes of the first series were inadequate. In the second place, because of the observations of Langford *et al.* (1953) and Backett and Johnston (1959), a greater incidence of accidental injuries was expected in the families of these children than in a control group.

The patients of the control group were chosen to match the age and sex of the patients with head injuries. The 60 children of these two groups were called the index cases. It was found in retrospect that the two groups were very similar with regard to a number of other general features (Table 4). There were few differences in the informant's kinship to the index cases, the informant's own estimates of their housing conditions or the social class of the children in each group as judged by the occupation of the father.

TABLE 4

COMPARISON OF AGE, SEX, INFORMANTS, HOUSING AND SOCIAL CLASS OF ACCIDENT AND CONTROL GROUPS OF THE SECOND SERIES

	Head Injury Group	Control Group	Totals
Sex:			
Boys ..	20	20	40
Girls ..	10	10	20
Age group:			
0-4 years ..	9	9	18
5-9 years ..	13	13	26
10-13 years ..	8	8	16
Informants:			
Both parents ..	14	14	28
Mother ..	14	12	26
Father ..	2	3	5
Sister ..	0	1	1
Housing:			
Unsatisfactory ..	6	5	11
Satisfactory ..	24	25	49
Social class:			
I and II ..	3	8	11
III ..	15	10	25
IV and V ..	12	10	22

TABLE 3
DISTRIBUTION OF 1,180 CASES OF HEAD INJURY AMONG 1,155 PATIENTS

No. of Head Injuries	Number of	
	Children	Cases
1	1,136	1,136
2	14	28
3	4	12
4	1	4
Totals	1,155	1,180

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TABLE 5
COMPARISON OF PAST AND FAMILY HISTORY OF INJURIES IN ACCIDENT AND CONTROL GROUPS OF THE SECOND SERIES

	Head Injury Group	Control Group	Total	χ^2	Value of p
1. Index cases:					
No. of individuals	30	30	60	—	—
No. with past history of injury	13	10	23	0.16	0.7-0.5
No. of injuries incurred	19	18	37	—	—
2. Siblings:					
No. of individuals	66	44	110	4.11	0.05-0.02
No. with past history of injury	6	9	15	2.04	0.2-0.1
No. of injuries incurred	8	10	18	1.46	0.3-0.2
3. Parents:					
No. of individuals	60	60	120	—	—
No. with past history of injury	31	26	57	0.28	0.7-0.5
No. of injuries incurred	46	39	85	0.42	0.7-0.5
4. Close family: (2 and 3)					
No. of individuals	126	104	230	1.92	0.2-0.1
No. with past history of injury	37	35	72	0.33	0.7-0.5
No. of injuries incurred	54	49	103	0.08	0.8-0.7
5. Remote family: (grandparents, parents' siblings, first cousins)					
No. of individuals	528	440	968	5.06	0.05-0.02
No. with past history of injury	42	40	82	0.24	0.7-0.5
No. of injuries incurred	57	50	107	0.02	0.9-0.8
6. Whole family: (1+4+5)					
No. of individuals	684	574	1,258	9.44	>0.01
No. with past history of injury	92	85	177	0.34	0.7-0.5
No. of injuries incurred	130	117	247	0.24	0.7-0.5

Results

The results are summarized in Table 5. Thirteen of the children with head injuries had a past history of injury, compared with 10 in the control group. The 13 children in the head injury group had had 19 injuries between them, and the 10 children in the control group had had 18 injuries. Neither of these differences is significant. Similar comparisons were made between the siblings of the index cases, their parents, their more distant relatives and combinations of these groups. No significant differences were found in the incidence of past injuries. There were significantly more siblings and relatives in the families of the head injury group.

Over a third of the 60 index children had a past history of injury. Twenty of these children were boys and three were girls. This is significantly ($\chi^2 = 5.38$; $n = 1$; $p \leq 0.02$) more boys than would be expected from the sex ratio of the rest of the series. There was a history of injury in nearly half of the parents, roughly a seventh of the siblings and a twelfth of the remote family.

Discussion

The incidence of head injuries in this series was found to vary with four main factors: sex, age, the month of the year and the time of day. The most important of these appeared to be the child's sex.

There were consistently more boys than girls in all situations that were examined. More boys had head injuries at each year of age, in every month of the year, on each day of the week and at each hour of the day. More boys suffered each particular type of accident. More boys had severe head injuries, repeated head injuries and a past history of other accidental injuries.

The ratio of boys to girls in the first series was 2.3 to 1. This might conceivably be due to an excess of boys over girls in the general population. In Sheffield, however, the ratio of boys to girls is only 1.05 to 1 (Registrar-General, 1951), so that this can only account for a small fraction of the preponderance of boys with head injuries. Others have reported a similar sex incidence (Beekman, 1928; Ireland, 1932; Fabian and Bender, 1947; Rowbotham, Maciver, Dickson and Bousfield, 1954; Harris, 1957).

More boys had a past history of accidental injury than girls. This suggests that, in general, boys are more prone or liable to accidents than girls. This is borne out by mortality figures (van den Berg, 1957), hospital accident series (Simson, 1956), surveys of home accidents (Dennis and Kaiser, 1954) and other community studies (Jacobziner, 1955; Rice, Starbuck and Reed, 1956). This is not necessarily true for every type of injury because, for example, burns are commoner in girls

than in boys (Colebrook, Colebrook, Bull and Jackson, 1956).

A boy's relative proneness to head injury seems to vary with age. The ratio of boys to girls with head injuries steadily increased after the age of 2 years. However, as in other series (Ireland, 1932; Rowbotham *et al.*, 1954; Harris, 1957), the maximum incidence of cases was in the middle years of childhood. These two factors offset one another so that the commonest age for head injuries in boys was 5 to 9 years.

Seasonal variations in the incidence of fatal (van den Berg, 1957; Kanellakis, 1958) and non-fatal (DeCosse, 1953; Jacobziner, 1955) childhood accidents are well recognized. The greatest danger is in the summer months. The present series of head injuries conformed to the same pattern. There were no significant variations in the number of head injuries according to the day of the week, although both DeCosse (1953) and Ehrenpreis (1957) have reported low incidences of accidents in general on Sundays compared with the rest of the week.

Marked variations occurred in the time of day the accident happened. Peak periods were at noon and at 5 to 6 p.m. There were considerable differences between boys and girls and between the age groups in this respect. Most of the variation was due to variations in the numbers of boys. Corresponding variations did occur in the numbers of girls but these were small and only proportional in the 0 to 4 year old group. The most marked variations occurred in the numbers of 5 to 9 year old boys. Similar hourly variations have been noted for childhood accidents in general (DeCosse, 1953; Ehrenpreis, 1957). Ehrenpreis states that, in Sweden, the peak periods correspond to the hours before the main mealtimes and he suggests that more accidents happen because the children are more irritable, hungry and less well supervised. It would be of great interest, in this country, to see if the hourly accident pattern changed if milk were given out in schools in the afternoons instead of in the mornings.

Only a small proportion (1.6%) of children were represented more than once in the first series of head injuries. This, by itself, suggests that accident-proneness was of no great aetiological importance. On the other hand, it might be expected that accident-proneness would express itself differently at different ages. Affected children who have head injuries at the age of 5 to 9 years might have suffered burns, scalds or poisoning earlier in life. If accident-proneness is important in the aetiology of head injuries, one would expect a higher incidence of past injuries in a group of children with head injuries

than in controls. This could show itself in two ways. (1) There could be a greater number of children with a past history of injury. (2) Each group could have the same number of children with a past history of injury, but these children could have incurred a greater total number of injuries (i.e. they are accident-repeaters). No evidence of either of these situations was obtained from the second series of patients.

The second series revealed a high incidence of past injuries among children and their parents in both the accident and control groups. It was also found that the children with head injuries came from slightly larger families than the controls. In contrast to Langford *et al.* (1953) and Backett and Johnston (1959), no significant difference was found in the incidence of accidental injuries in the families of the two groups.

In conclusion, apart from increased liability associated with the male sex, no evidence of accident-proneness was discovered. This does not disprove the existence of accident-proneness nor discount its possible importance in the individual case. It does suggest that accident-proneness is of little significance in the aetiology of the great majority of head injuries in childhood.

Adelstein (1952) has critically reviewed the whole subject of accident-proneness. He points out that much of the confusion is semantic and rests on the interpretation of an 'accident'. This can mean death, a major injury, a minor injury or no injury at all but only damage to property (a mishap). It has been assumed (Newbold, 1926; Heinrich, 1941) that these events are closely related and that, for instance, the causes of mishaps or minor injuries are essentially the same as the cause of major injuries and fatalities. This premise is probably inaccurate. For example, in industry, there is only a very low correlation between minor and major injuries (Farmer and Chambers, 1926; Adelstein, 1952). In childhood, the age distribution of non-fatal accidental poisoning is different from that of fatal accidental poisoning (Clements, 1956). There is little correspondence between the causes of accident morbidity and the causes of accident mortality in childhood (Ehrenpreis, 1957). Observations on one type of accidental result (e.g. mishaps, death or a particular injury) do not necessarily apply to another. Adelstein himself found some evidence of accident-proneness in the aetiology of mishaps but little or none in the aetiology of major injuries.

The outstanding objection to the psychological explanations of accident-proneness is that they are based on such dubious evidence. Theories have largely been built up on the patient's view of the

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cause of his accident, weeks, months or years after it has happened.

It has been remarked that preoccupation with accident-proneness may well divert attention from other more rewarding aspects of accident causation. These include not only the effects of age, sex and season but also the means whereby a child learns to avoid accidents (Editorial, *British Medical Journal*, 1959).

Summary

Two series of children with head injuries were studied. The first series consisted of 1,180 cases admitted to a children's hospital over a period of seven years. The ratio of boys to girls was 2.3 to 1. The maximum incidence of cases was in the middle years of childhood. More cases occurred in the summer than the winter months. There was no significant variation in the number of cases according to the day of the week. Two peak frequencies occurred during the day, one at noon and a larger one at 5 to 6 p.m. Falls were the commonest type of accident. Only 1.6% of the children had more than one head injury; none had more than four.

In the second series, 30 children with head injuries were matched by age and sex with 30 acute medical cases. No difference was found in the incidence of accidental injuries in the past or family histories of these two groups. A third of the children, and half their parents had a history of accidental injury. The children with head injuries came from slightly larger families.

These findings are discussed. No evidence of accident-proneness was found apart from increased liability associated with the male sex.

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ABNORMALITIES OF VENTILATORY CAPACITY IN CHILDREN WITH ASTHMA AND BRONCHIECTASIS

BY

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It is now generally accepted that patients with pulmonary diseases frequently suffer from an impairment of ventilatory capacity and that much of their disability is connected with this. A number of methods have been devised to measure the ventilatory capacity, which all depend on measuring the maximum volume which can be ventilated in a given time. It can be done directly by persuading the subject to hyperventilate maximally and measuring the volume of gas expired in 15 sec. or some other part of a minute. This is the direct Maximum Breathing Capacity (M.B.C.)† and it can be performed at a pre-determined rate to a metronome, or at a rate of the subject's own choice. The result is expressed in litres per minute.

A different approach to measuring the same function has been to analyse a single fast maximum expiration against time and take that part of the volume expired in the first second or part of a second, as a measurement of ventilatory capacity. This measurement was introduced about 10 years ago (Tiffeneau, Bousser and Drutel, 1949; Gaensler, 1951) and has since then come into general use. It is termed the Forced Expiratory Volume (F.E.V.) and the time interval referred to is indicated in seconds as a suffix (e.g. F.E.V._{1.0}, F.E.V._{0.75}).

Kennedy and his colleagues have used the 0.75 sec. volume (Kennedy, 1953) but the 1.0 sec. volume introduced by Tiffeneau *et al.* (1949) has probably become more generally accepted as a standard measurement (Gandevia and Hugh-Jones, 1957).

The original justification for using a timed fraction of the forced vital capacity (F.V.C.) as an estimate of the ventilatory capacity, depended on the concept that this fraction represented that part of the vital capacity which was actually used during hyperventilation, the 'capacité pulmonaire utilisable à

l'effort' of Tiffeneau *et al.* (1949). Thus, if the duration of expiration and inspiration were equal, the one second F.E.V. would be the tidal volume of the Maximum Breathing Capacity performed at a respiratory rate of 30 per min., and the 0.75 sec. F.E.V. would be the tidal volume at a rate of 40 per min. The relationships are more complex than these concepts imply as the times taken for inspiration and expiration are different and the limit of inspiration varies at different rates of breathing (Bernstein and Kazantzis, 1954). In fact, the correct factor by which the F.E.V._{1.0} should be multiplied for prediction of the M.B.C. is 37.5 (Cara, 1953).

In this study the ventilatory capacity is measured in terms of F.E.V._{1.0} and nothing seems to be gained from the practice of converting these values to an indirect M.B.C., except that normal values for the latter are better known. In children, this does not apply and, therefore, in this study values of F.E.V._{1.0} are given unaltered. The Forced Vital Capacity (F.V.C.) is measured at the same time as the F.E.V._{1.0} and from them a ratio termed the F.E.V. % is derived, i.e. $\frac{\text{F.E.V.}}{\text{F.V.C.}} \times 100$.

Very few studies of ventilatory function have been done in children. Kennedy and his colleagues (Kennedy and Thursby-Pelham, 1956; Kennedy, Thursby-Pelham and Oldham, 1957; Thursby-Pelham and Kennedy, 1958), have studied the ventilatory capacity of normal and asthmatic children using the F.E.V._{0.75}. (These authors, using a different terminology, refer to this as the Expiratory Flow Rate—E.F.R.) Engström, Karlberg and Kraepelin (1956) have studied the static lung volumes of normal children and Helliesen, Cook, Friedlander and Agathon (1958) the static lung volumes and the mechanical properties of the lungs of normal children. Earlier studies such as that of Stewart (1922) were confined to measurement of the vital capacity.

In initiating an investigation of pulmonary

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† The terminology and abbreviations are those recommended by the Thoracic Society (Gandevia and Hugh-Jones, 1957).

function it seemed of importance to find tests which would evoke the cooperation of children and which would measure functions which were, in fact, altered in the chronic pulmonary diseases of childhood. The Forced Expiratory Volume in one second (F.E.V.₁₋₀) had the advantage that it could be measured very simply in a way which is interesting for children.

In a previous investigation (Strang, 1959) 418 healthy schoolchildren were studied and normal standards for F.E.V.₁₋₀, F.V.C. and F.E.V.% obtained. The F.E.V.₁₋₀ was best correlated with standing height, and a regression on the cube of the height with intervals of two standard deviations, derived from this study, provides normal standards for all comparisons in this paper. These are applicable equally to boys and girls.

The present investigation is intended to determine the circumstances in which the Ventilatory Capacity, in terms of the F.E.V.₁₋₀, is lowered, its discrimination as a clinical test and the ways in which the measurement can be used in the management and investigation of bronchitis in childhood.

Clinical Material and Methods

Serial readings of F.E.V.₁₋₀ were made on 59 children with chronic pulmonary diseases. Two groups were examined: 20 with asthma and 39 with bronchiectasis.

Asthma. Twenty children had the syndrome of recurrent dyspnoea, wheezing and cough which is usually termed asthma. All of them had a persistent eosinophilia in the peripheral blood, and none of them had evidence of bronchiectasis. Three of these patients produced purulent sputum from which *H. influenzae* was cultured and eight of the others had mucoid sputum intermittently. This group of patients were examined repeatedly (237 examinations) during the period from July, 1958 to February, 1959 and 14 of them were seen at two-weekly intervals during this period, with the exception of 26 planned examinations which were missed due to holidays, illness and other minor events.

At the beginning of the study general clinical data relating to each child were recorded, including the height, weight and age. At each subsequent visit the following information was also recorded, the clinical signs being classified into four arbitrary grades as follows—(0) Cough absent, no chest signs; (1) Cough present, no chest signs; (2) Cough present, scattered rhonchi audible in some parts of the lungs; (3) Cough present and rhonchi audible in all parts of the lungs. In the group of patients examined at two weekly intervals, the number of attacks of wheezing in the previous 14 days, the number of days since the last attack and the presence or absence of dyspnoea on exertion, were also recorded.

The clinical data were entered on specially prepared forms which provided space for the recording of each of the factors. At each visit the clinical assessment was recorded before the ventilatory measurement was made

and usually the clinical and ventilatory observations were made by two different people working in different rooms.

Bronchiectasis. Thirty-nine patients with the clinical picture of chronic pulmonary infection and expectoration of purulent sputum, were examined. All of these patients had persistent abnormal segmental shadows on plain radiographs of the chest and in 35 the presence of bronchiectasis had been confirmed by bronchography. None of them had eosinophilia. Serial observations were made (209 examinations) but these were less frequent than in the group with asthma as a less marked variation from time was expected.

The following clinical information was recorded for each patient.

- (a) The height and weight and age.
- (b) The clinical severity in three general grades as follows: (1) No obvious disability other than cough and sputum. (2) Cough and sputum; and in addition, general health interrupted by one or more febrile spells or other episodes of illness each year. (3) Cough and sputum with either dyspnoea or frequent febrile episodes or considerable loss of schooling, so that the child cannot live a normal life at any time.
- (c) A note was made of the diffuseness of râles or rhonchi on auscultation of the chest and divided into the following categories of diffuseness. (1) Signs, unilateral and localized. (2) Signs, bilateral and localized (usually basal). (3) Signs disseminated in all parts of the lungs.

A radiological assessment of the extent of the condition was made by examining plain films and bronchograms and making an estimate of the numbers of bronchopulmonary segments containing an abnormal shadow or deformed bronchus. Thirty-two patients had bronchograms which were considered adequate for this count but as the numbers counted on the plain film and on the bronchogram did not always correspond, the larger value in each case was taken as indicating the radiological extent.

The allocation of patients into grades of diffuseness and severity was done by two observers working together with the clinical records of the patients. Some of the ventilatory data had been collected at this time but it was not before them when the assessment was made. The radiological assessment was made with a radiologist who had no knowledge of the ventilatory results.

Testing Procedure. The child was taught how to make maximum fast expirations into a spirometer with a light aluminium bell similar to that described by Bernstein, D'Silva and Mendel (1952), which recorded on a drum revolving at 2 cm. per second. One cm. vertical movement of the bell was equivalent to a volume of 200 ml. so that the recording pen described a time—volume graph of the forced expiration similar to that shown in Fig. 1. After a number of practice attempts, three recordings were made from which mean values of the F.E.V.₁₋₀ and the F.V.C. were calculated. These volumes were corrected to 37° C. and the F.E.V.%, i.e. $\frac{\text{F.E.V.}}{\text{F.V.C.}} \times 100$

calculated. In the previous study of normals, 95% of repeated readings of F.E.V.₁₋₀ were within 3.8% of the individual's mean value.

Each child was examined clinically at the same time as the ventilatory measurements were made. All the children were receiving medical treatment of some kind. The group of 14 children with asthma, who were seen fortnightly, were taking part in a controlled drug trial and each of them was having choline theophyllinate in high dosage during three months of the observation period.

Results

Normal Pattern. Fig. 1 is typical of tracings which were obtained from normal children. The full height of the tracing represents the Forced Vital Capacity (F.V.C.) and the distance between the onset of expiration and the one second point represents the Forced Expiratory Volume in one second (F.E.V.₁₋₀). In normal children the absolute values of F.E.V.₁₋₀ and F.V.C. depend on the child's size, but the shape of the curve is constant. This is conveniently expressed as the ratio, $\frac{\text{F.E.V.}}{\text{F.V.C.}} \times 100$ or F.E.V.%. In a study of normal children (Strang, 1959) the mean F.E.V. % was 85% (S.D. 5.8) in boys and 89% (S.D. 5.4) in girls.

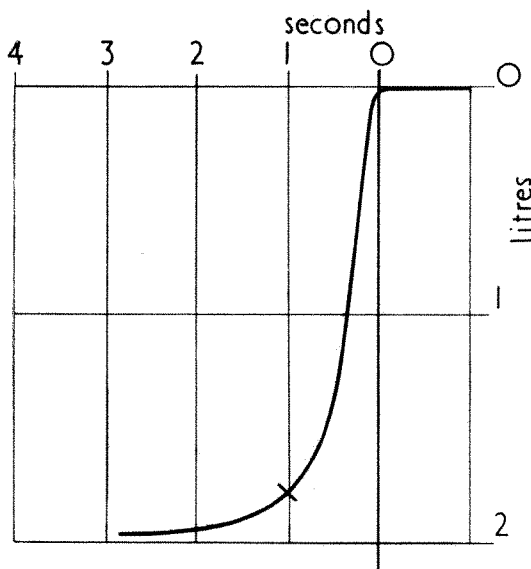


FIG. 1.—Spirometer tracing of maximum forced expiration. Normal child: standing height—53 in.

Abnormal Patterns. The types of abnormal tracing obtained were similar to those described by Thomson and Hugh-Jones (1958) in adult patients. In Fig. 2, three abnormal tracings have been superimposed on that of a normal child, all of the children

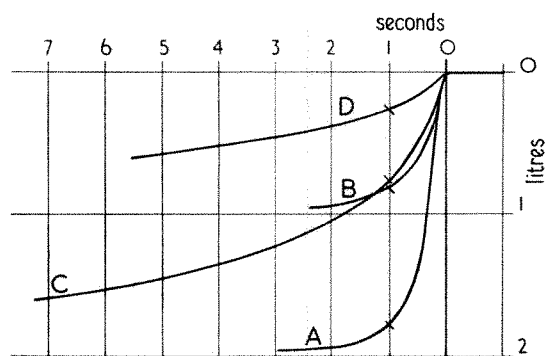


FIG. 2.—Superimposed spirometer tracings of a normal child and three children with chronic pulmonary disease, all 53 in. in height.

being of the same height and, therefore, comparable. A was from a normal child, B from a child with diffuse pulmonary fibrosis due to pulmonary haemosiderosis and C and D from children with asthma. The shape of the curve B was similar to the normal, the F.E.V.₁₋₀ and F.V.C. being reduced in proportion. This fact is expressed in a normal F.E.V.%. B was of the pattern expected in a restrictive lesion of the lungs or chest wall in which the extent of movement was limited but not its rate. The abnormal shape of curve C was due to a lesion which restricted the rate of movement of the chest, but its total volume only slightly. This was the pattern expected due to bronchial obstruction or diminished elastic recoil of the lungs. The F.E.V.₁₋₀ was reduced to a much greater degree than the F.V.C. and the F.E.V.% was much lower than normal. Curve D was a similar pattern but more severe. In this case, the F.V.C. and F.E.V.₁₋₀ were both diminished but this was more marked for the F.E.V.₁₋₀ than for the F.V.C.

In each case the F.E.V.₁₋₀ was a measurement of ventilatory capacity and the F.E.V.% gave an indication of the cause of the ventilatory impairment.

Results in Children with Asthma. In order to allow comparison between variable clinical factors and the pooled F.E.V.₁₋₀ results, the latter were converted to a percentage of the mean normal value for the child's height. The pooled results in this group showed a significant discrimination between each of the grades of physical signs (Fig. 3); between the presence and absence of dyspnoea on exertion (Fig. 4) and between whether or not there had been an attack of wheezing in the previous 14 days (Fig. 5); there was no difference between one and more than one attack in this period (Fig. 5) and the number of days since the attack was not apparently

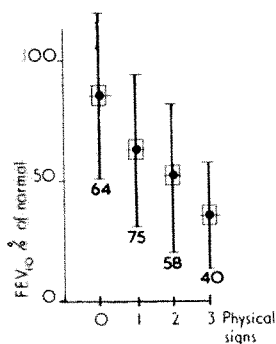


FIG. 3. Asthma. Pooled results of F.E.V. as per cent of normal compared with physical signs on auscultation (20 patients, 237 readings). Black circles indicate means, vertical lines indicate two standard deviations about the means; rectangles indicate two standard errors of the means; numbers refer to number of observations in each group. Where the rectangles do not overlap there is a significant difference between the means.

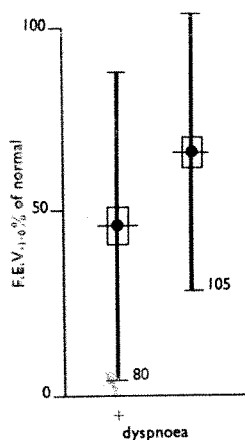


FIG. 4. Asthma. Pooled results of F.E.V. as per cent of normal compared with presence or absence of dyspnoea on exertion at that time. (14 patients, 185 readings.) Symbols and significance as in Fig. 3.

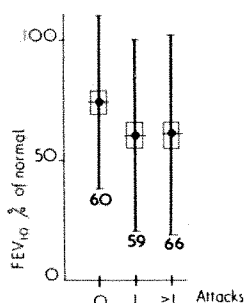


FIG. 5. Asthma. Pooled results of F.E.V. as per cent of normal compared with number of attacks of wheezing in previous 14 days. (14 patients, 185 readings.) Symbols and significance as in Fig. 3.

significant (0-3 days since attack—mean F.E.V. 59%, (n=78): >3 days since attack—mean F.E.V. 65%, (n=47): S.E. of difference between means=5.5).

There was a marked difference between readings of F.E.V._{1.0} at different times on the same child, the coefficient of variation about the individual means

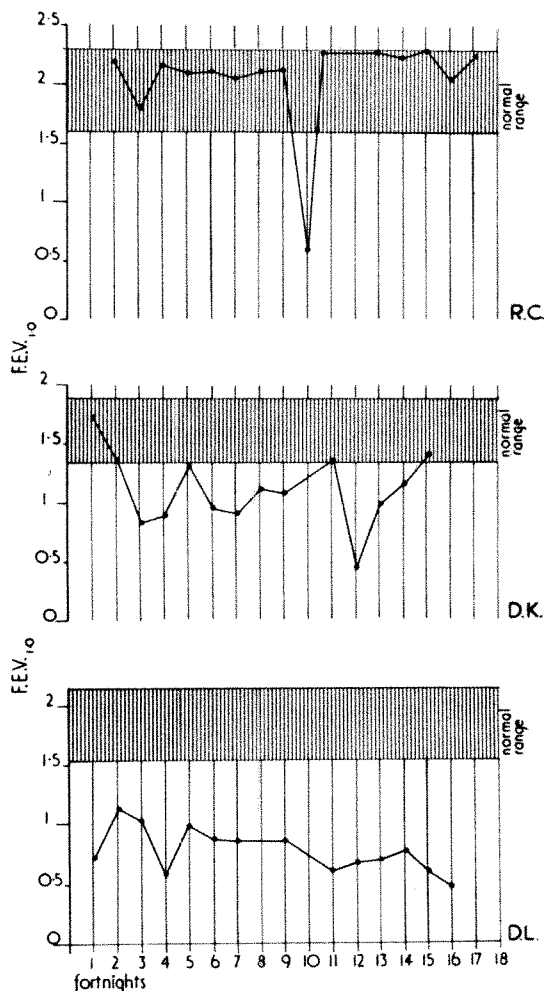


FIG. 6. Asthma. Serial records of F.E.V. in three children.

being 27%. The actual usefulness of the measurement was most evident in serial recordings in individuals such as shown for three children in Fig. 6. The top record is from a child who was in the normal range of ventilatory capacity most of the time but had a short-lived episode of abnormality. The middle record is of a child who was occasionally within the normal range, in this respect, but more frequently below normal. The lowest record is of a

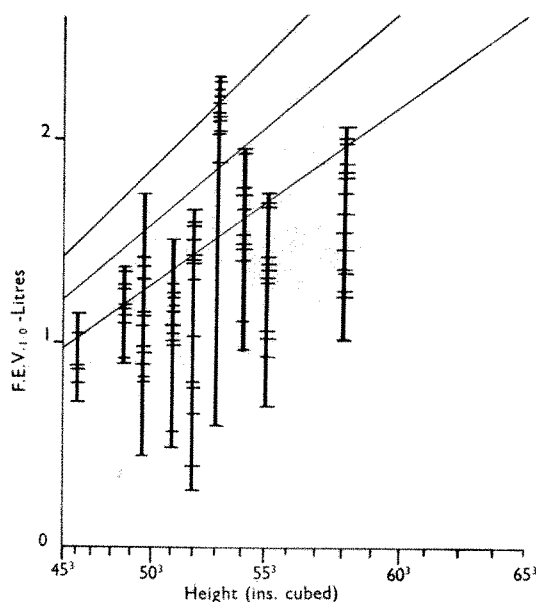


FIG. 7. Asthma. Serial readings of F.E.V. in nine children compared with normal limits, for height. Each child represented as a vertical line and different readings of F.E.V. by short horizontal lines.

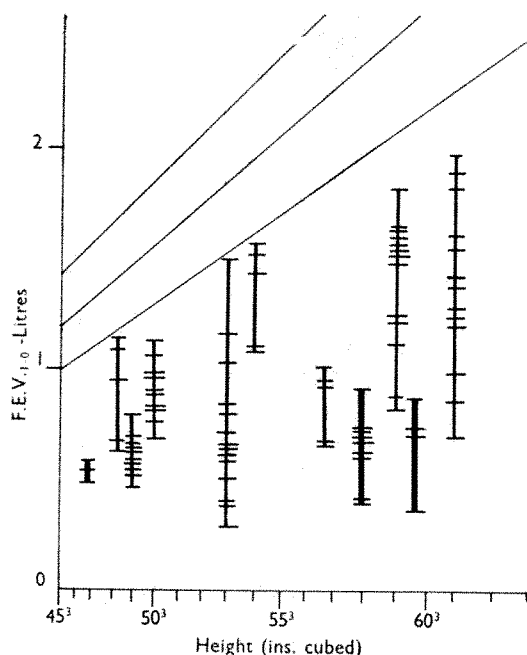


FIG. 8. Asthma. Serial readings of F.E.V. in 11 children compared with normal intervals for height. Each child represented as vertical line and different readings of F.E.V. by short transverse lines. Thick vertical lines represent children with purulent sputum.

child who had a persistently and severely impaired ventilatory capacity throughout the observation period.

The serial records of the 20 children are summarized in Figs. 7 and 8 and compared with the normal limits for height. Nine of these patients were never within the normal during the period of observation (Fig. 8), and particularly severe ventilatory defects were present in the three asthmatic children who also had purulent sputum.

The differences in ventilatory capacity between different children were evidently marked but not readily correlated with clinical data. The mean of the F.E.V.s recorded for each child was compared with the child's height and weight and with the persistence or otherwise of cough. These were the only reasonably permanent clinical characteristics which could be defined in this group.

The mean height was 97.8% (S.D. 7.95) of normal.* The mean weight was 83% (S.D. 13.8) of normal and there was no significant correlation between weight (per cent normal) and F.E.V. (per cent normal) ($r=0.184$; $n=20$). Nine patients had cough on each occasion they were seen and, in 11, cough was absent on one or more occasions, and between these groups the difference in F.E.V._{1.0} was significant. (Cough persistent mean F.E.V. (per cent normal) = 49.7. Cough not persistent mean F.E.V._{1.0} (per cent normal) = 70.08; $t=2.35$; $p>0.05$.)

Relationship of F.E.V._{1.0} and F.V.C. (F.E.V.%) in Asthma. Usually a reduction of F.E.V._{1.0} below normal was proportionately greater than the associated reduction of F.V.C. and this produced tracings similar to C and D in Fig. 2, in which the F.E.V.% was reduced. These changes were regarded as largely due to bronchial obstruction. In Fig. 9 the relationships of F.E.V._{1.0} and F.V.C. in these patients is presented. The diagonal line represents the relationship which would exist if the form of the spirometer tracings were normal and in purely restrictive lesions the results could be expected to fall about such a line. The quadratic regression line indicates the trend of the actual data and can be taken to show the changes likely to occur in a severely affected child during treatment or spontaneous improvement. In the low ranges, the F.E.V._{1.0} increases less markedly than the F.V.C.; they then increase at equal rates and the normal range of F.V.C. is reached before that of the F.E.V._{1.0}. Finally the F.E.V._{1.0} increases with relatively small change in F.V.C., reaching first the normal range

* The normal heights and weights were taken as the mean heights and weights for age from the charts prepared by Dr. P. E. Polani for the National Spastics Society.*

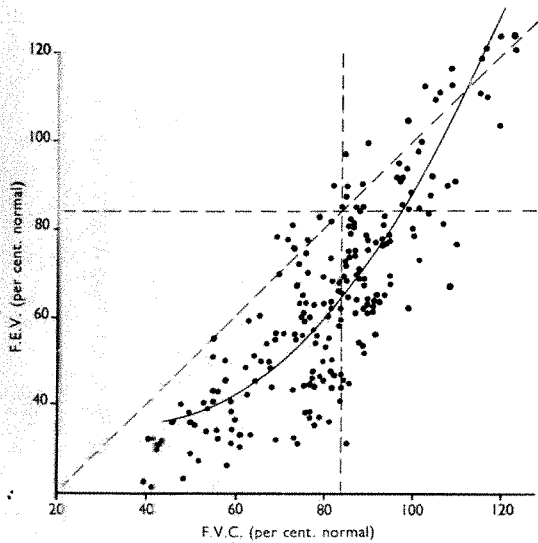


FIG. 9. Asthma. Relationship of F.E.V. as per cent of normal and F.V.C. as per cent of normal (20 patients, 237 readings). Diagonal interrupted line is relationship of F.E.V. and F.V.C. in spirometer tracings of normal shape. Horizontal and vertical interrupted lines show lower limits of normal for F.E.V. and F.V.C. Continuous line is quadratic regression fitted to data. ($F.E.V. = 57.11 - 1.08 \times F.V.C. + 0.0138 \times F.V.C.^2$; F.E.V. and F.V.C. as per cent of normal for height.)

for $F.E.V_{1-0}$ and finally the normal $F.E.V./F.V.C.$ ratio.

Results in Patients with Bronchiectasis. The variation in $F.E.V_{1-0}$ at different times in individual patients was less than in children with asthma, the coefficient of variation about the individual means being 12%. Many children had abnormally low $F.E.V.s$ on serial recordings as compared with the normal for height (Fig. 10).

In order to allow comparison with clinical factors, the $F.E.V_{1-0}$ was expressed as a percentage of the normal for height. Clearly definable clinical variations, from time to time during the observation period, were not very obvious in these patients, so that a comparison of variations in chest signs and similar factors with the pooled data was not relevant. For this reason, comparisons were confined to clinical differences between patients and the mean $F.E.V_{1-0}$ of each.

The mean height of the group was 97% (S.D. 4.7) of normal. The mean weight was 85.6% (S.D. 10.9) of normal, but there was no significant correlation between $F.E.V_{1-0}$ (per cent normal) and weight (per cent normal) ($r = 0.069$, $n = 39$). The results in the three grades of general severity were not significantly different (Table 1). The diffuseness of physical signs showed no difference between the

TABLE 1

BRONCHIECTASIS. COMPARISON OF F.E.V. (PER CENT OF NORMAL) WITH GRADE OF GENERAL CLINICAL SEVERITY

Grade of Severity	No. of Patients	Mean F.E.V. (% normal)	t	p
1	11	72.3	0.288	> 0.05
2	21	70.5		
3	6	63.2	0.85	> 0.05

TABLE 2

BRONCHIECTASIS. COMPARISON OF F.E.V. (PER CENT OF NORMAL) WITH DEGREE OF DIFFUSENESS OF SIGNS ON AUSCULTATION

Degree of Diffuseness	No. of Patients	Mean F.E.V. (% normal)	t	p
1	13	74.3	8.25	< 0.05
2	14	73.1		
3	12	57.5		

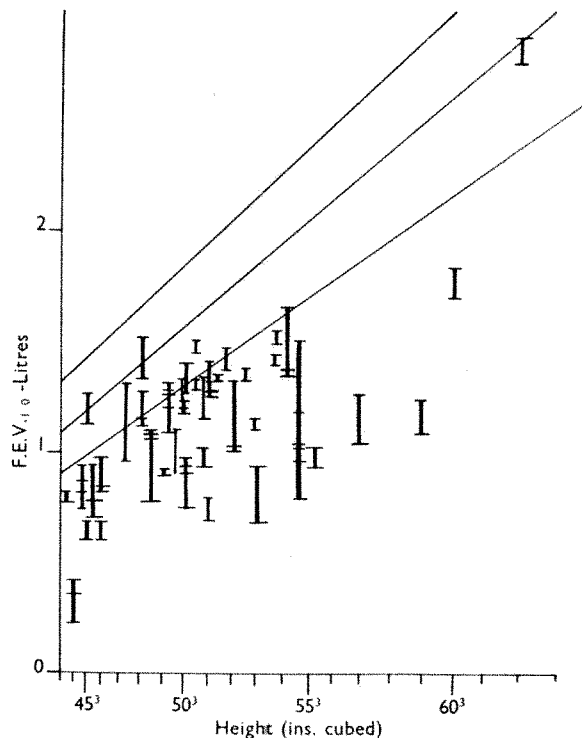


FIG. 10. Bronchiectasis. Serial readings of F.E.V. in 39 children compared with normal limits for height. Each child represented as vertical line and different readings of F.E.V. by short horizontal lines.

first two categories but there was a significantly lower mean in the third category (Table 2). The numbers of affected segments in the radiological

assessment ranged from two to 13 but the correlation with F.E.V.₁₋₀ was not significant ($r=0.24$, $n=32$).

F.E.V./F.V.C. Relationship (F.E.V.%) in Bronchiectasis. The relationship of F.E.V.₁₋₀ and F.V.C. in these patients was not so obvious as in children with asthma (Fig. 11). In general the trend was similar, reduction of F.E.V.₁₋₀ being proportionately greater than the reduction of F.V.C. The degree of this change was less marked, and in some cases the F.E.V.₁₋₀ and F.V.C. were reduced in equal proportions.

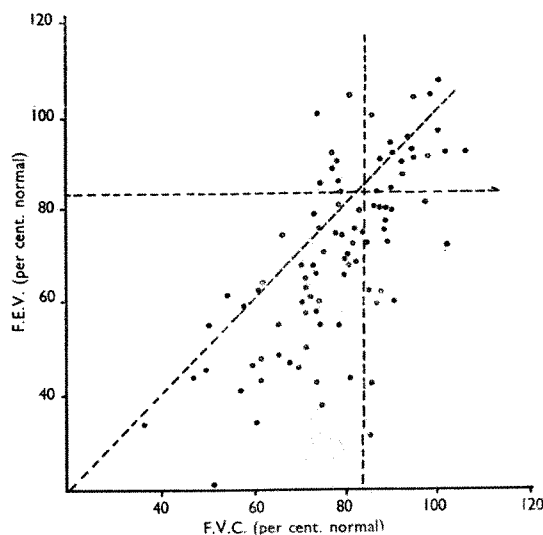


FIG. 11. Bronchiectasis. Relationship of F.E.V. as per cent of normal and F.V.C. as per cent of normal in 39 patients with bronchiectasis (209 readings). Lower limits of normal for F.E.V. and F.V.C., and diagonal indicating normal F.E.V./F.V.C. ratio, as in Fig. 9.

Discussion

Asthma. The severe ventilatory abnormalities in the children with asthma are reasonably closely related to clinical observations, but in the individual case it would be impossible to predict the degree of ventilatory impairment from clinical data, and in particular, serious impairment may be present in the absence of physical signs on auscultation. The usefulness of measuring the F.E.V.₁₋₀ is most obvious in the serial records of individual children and the most striking fact about most of these is the relatively continuous nature of the abnormality. Only rarely is it intermittent and the symptoms of overt wheezing arise more often as exacerbations of a chronic condition than from a previously normal ventilatory state.

A number of consequences appear to follow from the concept of asthma as a continuous sub-acute

condition. Treatment with anti-spasmodics or other agents might be expected to achieve optimum results when given continuously three or four times daily over long periods. The results of treatment of this kind would need to be assessed in terms of ventilatory capacity as a degree of impairment will persist after the disappearance of clinical signs. The aim will be to bring the F.E.V.₁₋₀ and F.V.C. into the normal limits and during such a development the relationship of F.E.V.₁₋₀ and F.V.C. might be expected to follow a trend similar to the regression in Fig. 9. Thomson and Hugh-Jones (1958) have described a similar relationship in adult asthmatics and have pointed out that the normal F.E.V.₁₋₀ for a particular patient has not been reached until the normal F.E.V./F.V.C. ratio (F.E.V.%) exists. This is important as the patient is likely to enter the normal range of F.E.V.₁₋₀ well before achieving his own particular normal value. Treatment cannot be regarded as wholly successful until a normal F.E.V.% has been achieved.

The persistence of an impaired ventilatory capacity in children over long periods may have a bearing on the natural history of the condition. It cannot be concluded that all of the patients who remained outside the normal limits of ventilatory capacity had permanent pulmonary damage; different treatment, in particular, inhalations of isoprenaline, might have improved some of them. Nevertheless, the possibility exists that a prolonged ventilatory abnormality, which is presumably associated with bronchial obstruction, may contribute to permanent pulmonary damage particularly if additional agents capable of damaging the lung are added to it. In this connexion it may be important that persistent cough was associated with lower values of F.E.V.₁₋₀ than when cough was intermittent, and that the three children with persistent cough and purulent sputum were very seriously affected.

Bronchiectasis. The frequency of ventilatory impairment in children with bronchiectasis was greater than expected. These abnormalities are probably due to factors causing increased stiffness of the lungs such as fibrosis and oedema, and also to bronchial obstruction, the latter being more important. Different tests would be necessary to elucidate these factors further.

Whatever the exact cause of the mechanical disorders of ventilation, they are likely to be due to a diffuse process rather than to localized bronchiectasis. The clinical counterpart of ventilatory impairment is not very obvious except in the case of diffuse signs on auscultation. Morbid anatomical

studies including those of Allison, Gordon and Zinnemann (1943) and Whitwell (1952) have shown that the disease may be extremely diffuse and may involve areas which appear normal on bronchography. It has also been known for a long time that patients frequently have persistent cough and sputum following the apparently complete resection of bronchiectatic areas. There is obviously a need for a study which includes pre-operative and post-operative ventilatory measurements, but it seems likely that many children with bronchiectasis may have a diffuse bronchial damage or bronchitis, and in so far as measurement of F.E.V._{1.0} and F.E.V. % may show this, it should enable detection of children unlikely to benefit from surgical resection.

Field (1949), in a study of bronchiectasis in children, claimed that 33% of children had attacks of wheezing similar to asthma. This observation has not been confirmed in this centre and this may be due to differences in material or in terminology. The presence of impaired ventilatory capacity, due in part to bronchial obstruction, could lead to wheezing in certain circumstances, so that the present finding narrows the difference between our observations and those of Field (1949) to one of degree. Measurement of F.E.V._{1.0} should place the phenomenon on a quantitative basis, thus allowing exact comparisons.

Summary

Measurements of ventilatory capacity, in terms of the F.E.V._{1.0} reveal persistent abnormalities in children with asthma and bronchiectasis. They appear to provide an objective means of assessing an important aspect of these conditions which cannot be accurately assessed on clinical examination.

Measurements of this kind seem readily applicable to assessing the natural course of these diseases and the effects of treatment.

I am grateful to Professor S. D. M. Court for encouragement and for his help in allocating patients with bronchiectasis into clinical groupings, to Dr. D. Ramage for the radiological assessment, to Miss V. Faghen for technical assistance, to Dr. P. Hugh-Jones for suggesting this approach and for his valuable criticism.

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MEASUREMENTS OF PULMONARY DIFFUSING CAPACITY IN CHILDREN

BY

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Since the early studies of the Kroghs (Krogh, 1915) a number of investigators have employed low concentrations of carbon monoxide (CO) in order to study the diffusing capacity of the lungs. Carbon monoxide is taken up avidly by red blood cells in the pulmonary capillaries as it has 210 times the affinity for haemoglobin that oxygen has. For this reason, during the breathing of low concentrations of CO the tension of this gas in the blood plasma may be regarded as zero. If this assumption is made the diffusing capacity of the lungs for CO (D_{CO}) can be derived from a knowledge of the mean alveolar CO concentration and the uptake of CO over a fixed time interval. Difficulties arise mainly in arriving at a valid figure for the mean alveolar CO tension and in controlling the variations in diffusing capacity which occur in differing states of rest or exercise. The diffusion velocities of carbon monoxide (CO) and oxygen (O_2) are proportional to the ratio of their solubilities and inversely proportional to the ratio of the square roots of their molecular weights. The diffusing capacities of the lung for CO and O_2 (D_{CO} and D_{O_2}) can be regarded as similarly related, the D_{CO} being converted to D_{O_2} by multiplying by a factor of 1.23 (Krogh, 1915).

A number of clinical methods have been devised for measuring the D_{CO} using either steady state or single breath methods (Filley, MacKintosh and Wright, 1954; Forster, Fowler, Bates and Van Lingen, 1954; Bates, Boucot and Dormer, 1955; Gilson and Hugh-Jones, 1955; Ogilvie, Forster, Blakemore and Morton, 1957). The values obtained in normals and in patients with pulmonary diseases differ depending on the method used, the greatest difference being between single breath and steady state procedures. Because of these discrepancies and for other reasons the exact significance of these methods and the differences between them is rather uncertain. Nevertheless, there is no doubt

that abnormalities affecting gas uptake in the lungs can be detected by one or other of them, and in approaching the general problem of pulmonary function testing in children it seemed reasonable to use a CO method in order to estimate the possible extent of gas exchange abnormalities in children with pulmonary disease.

It was preferred to use a method involving a minimum of discomfort for the child and no arterial punctures and for these reasons a method of Bates (*Bates et al.*, 1955) with some simplifications was employed.

In this method the CO tension of an end-tidal sample is taken as representing the mean alveolar tension of this gas.

Methods

Clinical Material. Four groups were examined: 79 normal children, 37 with bronchiectasis, 15 with asthma, and two with diffuse pulmonary disease.

The normal children were hospital in-patients and out-patients in whom cardiac and pulmonary disease had been excluded on clinical grounds. Thirty-five were girls, 44 were boys, and their ages were 5-14 years. Each child was tested on one occasion.

The 37 children with bronchiectasis were included in a previous study of ventilatory capacity abnormalities (Strang, 1960). All of them had cough, purulent sputum and abnormal segmental opacities on plain radiographs of the chest, and in 34 of them the presence of bronchiectasis had been confirmed on bronchography. Fifty-eight measurements of D_{CO} were performed, 16 of the children being tested on two or more occasions. To allow comparison of functional and clinical data these patients were allocated to three grades of severity of symptoms and into three categories of increasing diffuseness of râles or rhonchi on auscultation of the chest. An exact definition of the groups is contained in a previous paper (Strang, 1960). The child was allocated to the categories without knowledge of the results for D_{CO} . For comparison with radiological appearances a count was made of the numbers of bronchopulmonary segments seen to be involved on plain radiographs and bronchograms.

The 15 children with asthma were each tested on one

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occasion. Eosinophilia and impaired ventilatory capacity had been detected at some stage in each of them. None of them had permanent segmental shadows in plain radiographs of the chest but four of them habitually expectorated purulent sputum.

Of the two children with diffuse pulmonary disease one child had severe pulmonary infection associated with fibrocystic disease of the pancreas, and the other, idiopathic pulmonary haemosiderosis. The latter child had had repeated haemoptyses over a period of five years and radiological changes characteristic of the condition. Each of these children was tested on three separate occasions.

Apparatus and Procedure. The apparatus (Fig. 1) consisted of a 50 litre plastic bag A connected by a two-way tap and 0.75 in. diameter tubing to a 'Ruben' valve assembly B. This was fitted with a 'B.M.R.' mouthpiece and connected by tubing on the expiratory side to a 15 litre plastic bag C fitted with a two-way tap. The 'Ruben' valve was modified to include an Otis-Rahn end-tidal sampler D and this was connected by a sampling pump to a small 0.5 litre plastic bag E fitted with a two-way tap.

The bags were arranged on either side of a small table and the valve assembly and mouthpiece were attached to the table by an easily adjusted flexible clamp holder. During testing, the child sat comfortably at the table and, after a brief settling-down period, was connected to A which contained a prepared mixture of 0.1% CO in air. At the same time the Otis-Rahn sampler was connected to the pump operating at 250 ml. per min. After 1.5-2 min. to allow for clearing of the dead space of the apparatus and equilibration in the lungs, the expired gas was collected in C for 1 min. by a stopwatch. The end-tidal sample was collected over 1.5 min. which ensured an adequate size of sample. At the end of the procedure, the concentrations of CO in the inspired, expired and end-tidal samples were measured by passing through an infra-red

gas analyser,* and the volume of gas in bag C was measured by passing it through a gas meter.† The minute ventilation was taken as this volume plus the volume removed for sampling and the volume of the end-tidal sample.

From these readings the Dco (in ml./min./mm. Hg partial pressure difference of CO) was calculated according to the following expression, the tension of CO in the pulmonary capillary blood being taken as zero:

$$Dco = \frac{\dot{V}(FI - FE)}{FET. (B - 47)}$$

(where $\dot{V}$ is minute ventilation, FI, FE and FET, are fractions of CO in inspired, expired and end-tidal gas, and B is barometric pressure).

Each child was tested twice and the result expressed as a mean of the two readings. The amount of blood inactivated by conversion of haemoglobin to carboxyhaemoglobin was estimated to be in the order of 30-50 ml. for the whole procedure.

Results

Normals. The coefficient of variation of a single estimate of Dco was 10.2%. A significant positive correlation was found between Dco and the child's height, weight, surface area and age (Table 1). The correlation with surface area was better than with the other parameters tested but that with height was almost as good and the results are presented as a regression on the height with intervals of two standard deviations (Fig. 2).

TABLE 1

CORRELATIONS OF Dco WITH AGE AND VARIOUS BODY MEASUREMENTS (79 NORMAL CHILDREN)

	Correlation Coefficient (r)
Surface area	0.654
Height	0.635
Weight	0.620
Age	0.511

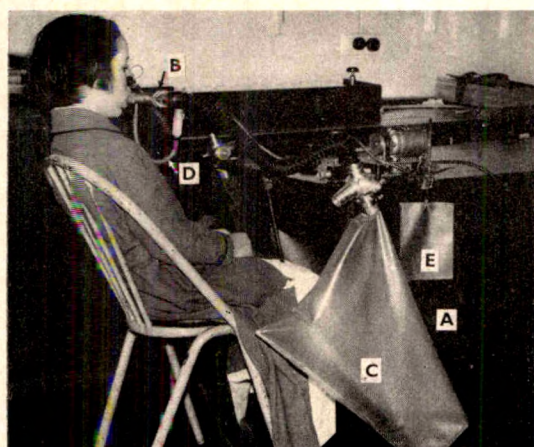


FIG. 1.—Apparatus for measurement of Dco—see text.

Bronchiectasis. The results in 34 children with bronchiectasis are shown in Fig. 3 and compared with the normal limits for height. Relatively few of these results were outside the normal limits but there was a trend towards lower values. This was shown in a significant difference between the mean of this group and the normals when both sets of data were expressed as a percentage of the normal mean for height. (Normal mean=100%, S.E.=2.17, n=79; Bronchiectasis mean=79%, S.E. 2.87, n=58.)

* Supplied by Sir Howard Grubb (Parsons) Limited.

† Supplied by Parkinson and Cowan Limited (Type C.D.4).

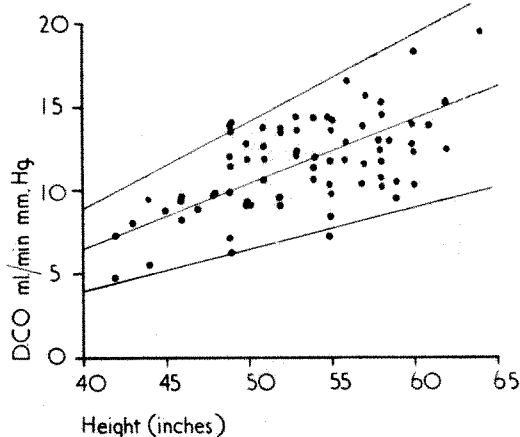


FIG. 2.—Dco of 79 normal children by height. 35 girls, 44 boys. Regression: Dco ml./min./mm. Hg = $0.390 \times \text{Ht. (in.)} - 9.1$. (Coefficient of variation between children = 19.3%. 95% limits shown.

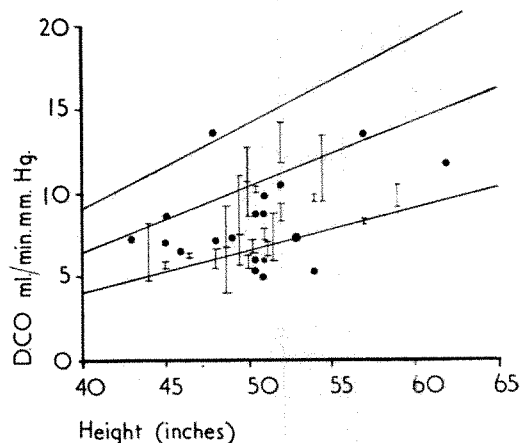


FIG. 3.—Dco of 37 children with bronchiectasis compared with normal limits for height. 58 observations. Repeated observations on one child are joined by a vertical line.

There appeared to be no significant relationship between Dco and the grades of severity or diffuseness of the bronchiectasis (Tables 2 and 3) and no obvious correlation with the numbers of abnormal segments counted on chest radiographs.

Asthma. The results are shown in Fig. 4 and compared with the normal limits for height. These patients were in differing states of ventilatory impairment, six of them having diffuse rhonchi on auscultation at the time of testing. The results,

however, showed no important difference from the normal and they were not analysed further.

Diffuse Pulmonary Lesions. The results on these two patients, each tested on three separate occasions, are shown in Fig. 5 and compared with the normal limits for height. The child with fibrocystic disease was within normal. The child with idiopathic pulmonary haemosiderosis had a severe impairment of diffusing capacity and this finding was highly repeatable.

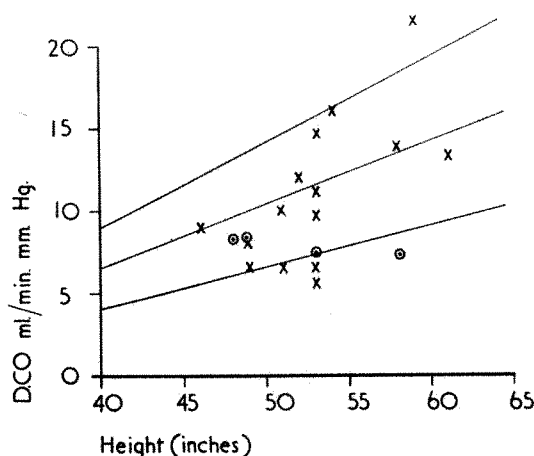


FIG. 4.—Dco of 15 children with asthma. Crosses represent children with no overt pulmonary infection. Circles represent children with purulent sputum.

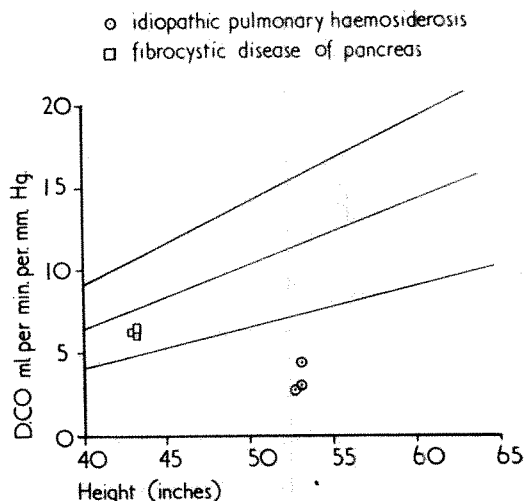


FIG. 5.—Dco in two children with diffuse pulmonary disease.

TABLE 2

Dco AND CLINICAL ESTIMATE OF SEVERITY OF BRONCHIECTASIS (59 OBSERVATIONS, 34 CHILDREN)

Grade of Severity	No. of Observations	Mean Dco (% normal)	t	p
1	18	81.6	0.337	>0.05
2	31	79.4		
3	10	72.0	1.065	>0.05

Discussion

The Method. The method used to measure Dco can be criticized on at least two grounds. First, it could not be ensured that the children were completely at rest or in comparable states of activity during the procedure and some of them tended to hyperventilate. Second, it is quite possible that the end-tidal sample did not represent a true mean of the alveolar gas, the poorly ventilated areas of lung probably being under-represented. Alternative means of arriving at this value include calculation from the arterial CO₂ tension (Filley *et al.*, 1954), calculation from the Bohr equation using an assumed value for the anatomical dead-space (Bates *et al.*, 1955) or the use of a single breath method after preliminary estimation of the functional residual capacity (Ogilvie *et al.*, 1957). The first of these was not used because arterial punctures were considered undesirable in these patients; the second could not be used because reliable data for anatomical dead-space are lacking in children. The third possibility was rejected because it was thought that the timing of breath holding would require too great a degree of cooperation.

Normal Values. The results in normal children are presented as a regression on the standing height because this appears to be a better basis for comparison between normals and children with pulmonary disease than the weight or surface area which is derived from the height and weight. This is because children with pulmonary disease are frequently below normal in weight but seldom in height (Strang, 1960). The height was used as a basis for comparison in previous studies of ventilatory capacity and this is an additional reason for using it here, particularly as the correlation is only slightly less good than that with surface area.

Results in Pulmonary Diseases. Significant abnormalities of diffusing capacity would appear to be rare in children. The only undoubted example detected in this study was in the child with idiopathic pulmonary haemosiderosis. This finding was highly repeatable and it is probable that other similar

TABLE 3

Dco AND DIFFUSENESS OF SIGNS ON AUSCULTATION (59 OBSERVATIONS, 34 CHILDREN)

Grade of Diffuseness	No. of Observations	Mean Dco (% normal)	t	p
1	19	84.2	1.49	>0.05
2	19	75.1		
3	21	76.4		

defects could be detected by this method. Diffuse infiltrative lesions of the lungs such as this are rare in childhood and the measurement of diffusing capacity is likely, therefore, to have a very limited application. It is certainly unlikely to be useful in studies of asthma and bronchiectasis.

The overall Dco measured by any steady-state technique such as the present one is dependent on the balance between ventilation and blood flow, and when inequalities of ventilation-bloodflow ratios exist, they will lead to lower values for the overall diffusing capacity, without there necessarily being any obstacle to diffusion in any individual part of the lung (Forster *et al.*, 1954). Bronchiectasis in children is a diffuse patchy condition (Whitwell, 1952) which might be expected to be associated with inequalities of ventilation and bloodflow, and it may be that the lower than normal values of Dco obtained in these children are due to this rather than to an impairment of diffusing capacity as usually understood. If this is so, an investigation of ventilation-bloodflow inequalities in this group might be rewarding.

Summary

Measurements of the diffusing capacity for carbon monoxide (Dco) in children are presented. The method appears to have a limited application in the study of pulmonary diseases in children.

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NORMAL STANDARDS FOR SINGLE BREATH TESTS OF VENTILATORY CAPACITY IN CHILDREN

BY

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Tests of ventilatory capacity based on the recording of a maximum forced expiration after a full inspiration are becoming increasingly widely used. They are quicker to perform and require less cooperation and effort on the part of the subject than the conventional maximum breathing capacity estimation, and the results are more informative because three indices of ventilatory capacity, each of different significance, are derived from the recording of this simple manoeuvre. These indices are: (1) the forced vital capacity, (2) the volume of gas expired over a given time interval (usually the first second or half second), and (3) the percentage of the vital capacity (or forced vital capacity) expired within the same time period (that is, 2 as a percentage of 1). In this department the procedure has been found most appropriate in paediatric work; the children learn it readily and can repeat it frequently with, in my experience, greater consistency than the maximum breathing capacity test.

Adequate normal standards are available for the vital capacity (Turner and McLean, 1951; Jones, 1955), and this paper provides data relating to the percentage of the vital capacity expired in the first second and half second of a forced expiration.

Definitions and Terminology

The recording obtained when the subject, after a full inspiration, forcibly and completely exhales into a spirometer, the movement of which is recorded with a kymograph, is termed the forced expiratory spirogram (F.E.S.). The volumes of gas exhaled in the first half second and the first second of expiration are termed the forced expiratory volume at half a second (F.E.V._{0.5}) and one second (F.E.V._{1.0}) respectively. The total volume of gas expired is termed the forced vital capacity (F.V.C.). The qualification 'forced' is added to distinguish this measurement from the vital capacity (V.C.) estimated in the conventional manner, that is, when the

expiration, in the earlier phases at least, is comparatively 'unforced'. The distinction is necessary because in certain pathological states the values for the vital capacity differ according to whether the expiration is forced or not; in emphysema, for example, 'air-trapping' leads to a forced vital capacity which is smaller than the vital capacity. The 'expired percentage' at 0.5 second or 1.0 second is the percentage of the V.C.* expired in the appropriate time interval and is abbreviated to F.E.V._{0.5}% or FEV_{1.0}%; it is therefore equal to $\frac{\text{F.E.V. } 0.5}{\text{V.C.}}$.

$$\times 100 \text{ or } \frac{\text{F.E.V. } 1.0}{\text{V.C.}} \times 100.$$

The terminology set out above is in accord with that adopted and recommended for general usage by the Thoracic Society of Great Britain (Gandevia and Hugh-Jones, 1957). It replaces or modifies a remarkable variety of different names employed by different workers in different countries for tests and their results which are essentially similar.

Methods

The spirometer used was of the type described by Bernstein and others (1952) to minimize various errors in the response of the bell to the sudden entry of gas. All connexions were of wide bore to reduce resistance to gas flow. The patient fitted a valveless anaesthetic mask, of adult or child size, with a one-inch outlet, to his face; a face mask has been found more convenient and less disturbing for the patient than the usual mouth-piece and noseclip. A Palmer kymograph was set to give a paper speed of 3.0 cm. per second. No timing device was employed during the recordings but the speed of the kymograph was periodically checked against a mechanical time-marker. Tracings were not begun until the drum had moved approximately 10 cm. One

* The F.V.C. is used by many workers in preference to the V.C. However, the latter is the more repeatable estimation and, in my view, the more fundamental characteristic. Numerically the difference is negligible except when there is significant 'air-trapping'.

centimetre of travel of the bell was produced by the entry of 300 ml. of gas; this calibration was carefully checked by direct measurement of the internal diameters of the bell throughout its length.

After their height* (without shoes) had been measured the subjects were seated at a comfortable height in relation to the spirometer. The tests were explained and the fit of the face mask demonstrated and checked. The V.C. was then estimated in the conventional manner. Several recordings of forced expiration were made. The number of recordings of vital capacity and of forced expiration varied from subject to subject; four 'satisfactory' recordings of vital capacity and three of forced expiration were required, the mean value of these estimates being accepted. By 'satisfactory' is meant a recording free of artefacts and of mistakes on the part of the subject as judged by eye. Misleading tracings due to misunderstanding or obviously incomplete co-operation were discarded. In most instances 'satisfactory' therefore implies reasonable consistency. The statistical criticisms of this procedure are appreciated but it was used because it must necessarily be the approach adopted in clinical practice. From two subjects (1.3%) it was found impossible to obtain satisfactory recordings. It was usual for the subject to have watched two or three of his colleagues do the tests before his turn came.

The values for F.E.V._{0.5}, F.E.V._{1.0} and the V.C. were derived from these tracings and F.E.V._{0.5}% and F.E.V._{1.0}%, with which this paper is primarily concerned, were calculated.

Children Studied. The children studied attended four government schools, two in an industrial area and two in residential suburbs. As the findings were similar in the two areas the results were pooled. A total of 91 males and 75 females between the ages of 5 and 14 years were examined; the numbers at each year of age are set out in Table 1. Care was taken to avoid selection on any obvious grounds, such as intelligence or physical prowess,

and volunteers were not called. The study was conducted in conjunction with the periodical examinations conducted by school medical officers. Children with asthma, chronic pulmonary infection, moderate or severe thoracic deformity and very occasional subjects with extremely poor posture and physique were excluded. Approximately 10% of the children were immigrants; their results were comparable with those of Australian children.

TABLE 1
AGE DISTRIBUTION OF SUBJECTS

Year of Life	Number of Patients	
	Female	Male
6	3	3
7	7	4
8	1	7
9	10-21	7-21
10	7	11
11	9	10
12	12	10
13	14	25
14	16-58	14-70
Total	79	91

Results

The correlation coefficients and regression equations relating F.E.V._{0.5}% and F.E.V._{1.0}% to age and standing height are set out in Table 2 for both the male and female series. In the latter there is a good correlation between F.E.V._{0.5}% and F.E.V._{1.0}% and each of the other parameters; all the correlation coefficients are significant at the 1% level. In the male series significant correlations are found only in relation to F.E.V._{0.5}%, while those for F.E.V._{1.0}% are virtually zero. The reason for this lies in the stability of F.E.V._{0.5}% and F.E.V._{1.0}% over the whole range of age or height in the boys, whereas in the

TABLE 2
CORRELATION COEFFICIENTS AND REGRESSION EQUATIONS FOR F.E.V._{0.5}% AND F.E.V._{1.0}% ON STANDING HEIGHT AND AGE

Procedure	Sex	r	Regression Equation	95% Tolerance Limits at Mean Values
F.E.V. _{0.5} % on standing height (S) (in.)	F	0.577**	F.E.V. _{0.5} % = 115.2-0.993 S	±16.6
	M	0.216*	F.E.V. _{0.5} % = 81.7-0.403 S	±20.8
F.E.V. _{0.5} % on age (A) (mth.)	F	0.547**	F.E.V. _{0.5} % = 85.0-0.193 A	±17.0
	M	0.273**	F.E.V. _{0.5} % = 72.7-0.105 A	±20.5
F.E.V. _{1.0} % on standing height (S) (in.)	F	0.372**	F.E.V. _{1.0} % = 113.9-0.561 S	±16.5
	M	0.063	F.E.V. _{1.0} % = 87.1-0.098 S	±17.8
F.E.V. _{1.0} % on age (A) (yr.)	F	0.336**	F.E.V. _{1.0} % = 96.2-0.104 A	±16.8
	M	0.053	F.E.V. _{1.0} % = 83.9-0.017 A	±17.8

Degrees of freedom: females, 77; males, 89; * significant at 5% level; ** significant at 1% level.

* Stem height was also measured but subsequent statistical analysis indicated that it offered no advantage over the simpler measurement of standing height in the prediction of any of the ventilatory indices. The results obtained in relation to stem height were similar in all respects to those for standing height.

girls there is a pronounced fall in both values. Fig. 1a shows the regression lines for the absolute values of F.E.V._{0.5}, F.E.V._{1.0} and V.C. on standing height for both sexes. The increase in V.C. with increasing

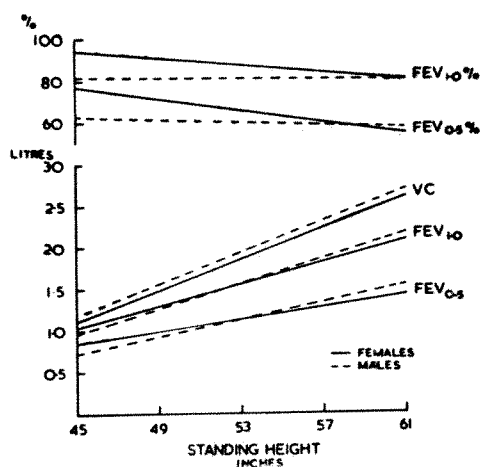


FIG. 1(a)—(lower graph)—Regression lines for absolute values of F.E.V. 0.5, F.E.V. 1.0 and V.C. on standing height for both sexes. FIG. 1 (b).—(upper graph)—Relates values for F.E.V. 0.5% and F.E.V. 1.0% (calculated from regression lines in Fig. 1(a)) to standing height for both sexes.

height is similar in girls (continuous lines) and boys (broken lines), but in the boys F.E.V. 0.5 and F.E.V. 1.0 increase more with increasing height and more in relation to the V.C. than is the case with the girls. This is reflected in the graph (Fig. 1b) relating values for F.E.V. 0.5% and F.E.V. 1.0%, as calculated from the regression lines in Fig. 1a, with standing height; the calculated values may be compared with the regression lines for the actual values (Figs. 2 and 3). Separate analysis of the results for children of 9 years of age and above and for children less than 9 years old revealed the same pattern of results in all groups as in the two series as a whole. There was therefore no evidence to suggest that lack of

cooperation on the part of the older girls or younger boys would serve as an explanation of the relative 'expiratory inefficiency' of those groups. Grouping by age according to the mean values for the ventilatory indices or according to the totals does not affect the findings set out above.

Results of multiple regression analysis showed that little was gained in the prediction of normal values by employing the regression line of F.E.V. 0.5% or F.E.V. 1.0% on both standing height and age. The influence of age is small relative to that of height and its inclusion does not materially reduce the tolerance limits. It may be added that further analysis of the absolute values of F.E.V. 0.5, F.E.V. 1.0 and V.C. in relation to standing height and age showed a similarly negligible effect of age.

Discussion

The results obtained for vital capacity in this survey are almost identical with those of other observers and hence the present paper is confined chiefly to a consideration of the values for the percentage of the vital capacity expired in the first half-second and first second of a forced expiration. In clinical work, prediction of normal values based on age alone is obviously unsatisfactory because it ignores the important factor of size. In the present study, as in others, age (over the range studied) was found to exert little effect on the several indices of ventilatory capacity compared with the effect of size as indicated by standing or stem height. Standing height is a simple and routine measurement in most paediatric clinics and, as stem height was found to offer no significant advantage, it forms an appropriate basis for the prediction of normal values.

In females F.E.V. 0.5% ranged from 70% at a

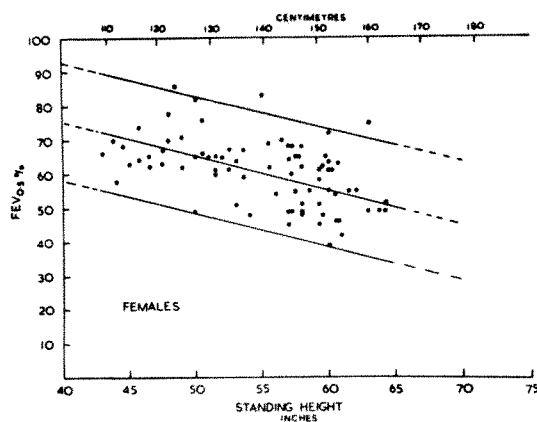


FIG. 2a.

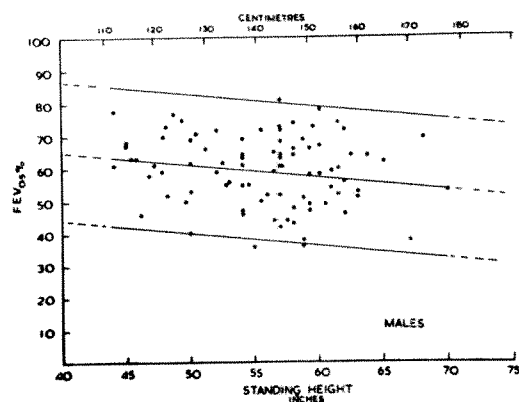


FIG. 2b.

FIG. 2.—Actual values for F.E.V. 0.5% plotted against standing height with regression lines and 95% tolerance limits: (a) females, (b) males.

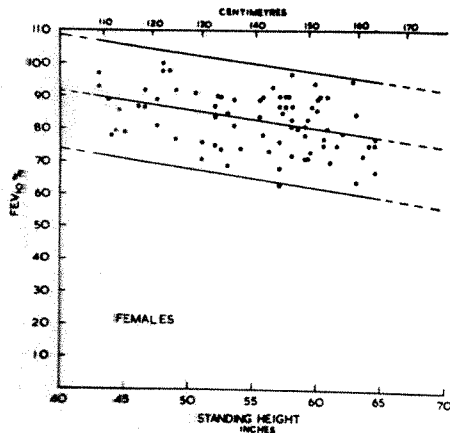


FIG. 3a.

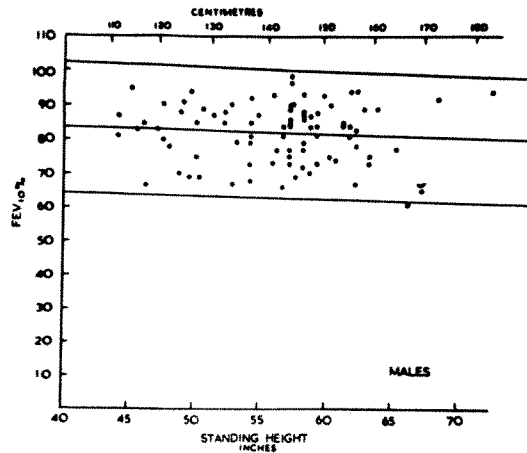


FIG. 3b.

FIG. 3.—Actual values for F.E.V. 1.0% plotted against standing height with regression lines and 95% tolerance limits: (a) females, (b) males.

height of 45 in. (114 cm.) to 50% at 65 in. (165 cm.) and F.E.V. 1.0% from 88% to 77% with 95% tolerance limits of $\pm 17\%$ in each case. In the males F.E.V. 0.5% ranged from 63% at 45 in. (114 cm.) to 55% at 65 in. (165 cm.) and F.E.V. 1.0% from 82% to 78% with 95% tolerance limits of $\pm 20\%$. As the increase of vital capacity with increasing height is similar in boys and girls the difference in behaviour is due to different 'rates' of increase in F.E.V. 1.0 and F.E.V. 0.5 with increasing height; in young boys the absolute values for these indices are lower than for girls (although the V.C. is higher) but over a height of about 4 ft. 6 in. the boys have the higher values (although the V.C. increase in boys and girls is the same). No explanation for this sex difference is apparent but it is worth noting (a) that the similarity of the line relating V.C. and height in boys and girls has been reported in other studies, and (b) that at the age of 14 years the present values for F.E.V. 0.5% and F.E.V. 1.0% are those regarded as normal for adults of both sexes. These observations, combined with the finding that the results are similar when the younger and older children are studied as separate groups, suggest that the difference between the sexes is a real one and is

not attributable to lack of cooperation on the part of any sub-groups in the performance of the vital capacity or forced expiration manoeuvres.

Summary

Indices of ventilatory capacity derived from the forced expiratory spiograms of a series of healthy school children are related to standing height.

Attention is drawn to certain differences between the sexes in regard to the proportion of the vital capacity expired in the first second or half-second of a forced expiration.

I am indebted to Dr. B. McCloskey and the School Medical Officers for their cooperation, and to Dr. Howard Williams for his interest in the project.

The statistical analysis was carried out in the Statistics Department of the University of Melbourne, notably by Miss Betty Laby, to whom my thanks are due.

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THE CEREBRO-OCULAR-RENAL DYSTROPHIES: A NEW VARIANT

BY

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Under this title it is proposed to describe a syndrome which has been under observation in two brothers, both of whom have now died. The syndrome is characterized clinically by anorexia, failure to grow, muscular hypotonia, corneal opacities and mental retardation; and physiologically by a severe hyperchloraemic acidosis, a very acid urine and a noteworthy defect on the part of the kidney to excrete ammonium ions. Progressive renal deterioration has been the cause of death. The disease thus belongs in a way to that ill-defined group described by Lowe, Terry and MacLachlan (1952), Royer and Prader (1957), Debré, Royer, Lestrade and Straub (1955) and also perhaps Goldbloom, Fraser, Waugh, Aronovitch and Wigglesworth (1957). It differs from all of them, however, in the nature of the renal lesion. It has been possible to make clinical, biochemical and post mortem investigations which will each to some extent be considered separately.

Clinical Histories and Biochemical Findings

The Family. The two patients were brothers, the only children of normal and unrelated English parents. A female sibling was stillborn. Their father has two healthy brothers; their mother a clinically normal sister. Forty other members of the family have been traced without finding any evidence or records of the syndrome.

Case 1 (M), a male child, was born on May 5, 1954. Pregnancy and delivery were normal. His weight at birth was 2.4 kg. and the circumference of his skull 32.5 cm. He was breast fed for three months, but from the start took his food badly, and showed an increasing tendency to vomit from the age of 3 months. He was brought to the hospital at Leicester on account of his eyes and there he was found to have corneal opacities, nystagmus and intense photophobia. He failed to reach the normal milestones and was considered very 'backward' and mentally retarded by the age of 6 months. He was, therefore, sent to a London hospital in Decem-

ber, 1955, where the diagnosis of blindness, corneal opacities and mental retardation was confirmed. Pneumo-encephalograms, however, disclosed no abnormality. His cerebrospinal fluid (C.S.F.), obtained 20 to 40 min. after the encephalogram was started, contained 110 mg. of protein/100 ml. and 40 cells/c.mm. His renal function was not investigated.

In November, 1956, he was admitted to Leicester Infirmary under W.J.M. for further investigation. By this time he had had one or two major convulsions. He had a little less photophobia but otherwise his mental and ocular abnormalities seemed unchanged. His reflexes were all active and normal. His systolic blood pressure was found to be 145 mm. Hg by the flush method, but a narrow cuff was used and this figure may have been too high. Blood was withdrawn for examination and the most striking finding was the low concentration of 'total CO₂'. Other results were—serum calcium 10 mg./100 ml. and alkaline phosphatase 12.4 King Armstrong units. The findings in the serum and urine a few months later are summarized in Tables 1 and 2 and will be discussed after the clinical histories. The child's renal tract was visualized satisfactorily by intravenous pyelography and appeared to be normal. His urine was consistently very acid and specific gravities of 1017-1018 were reached in concentration tests. Paper chromatography (Dr. H. Bickel) disclosed no abnormal amino-acids and this finding was confirmed a year later in another laboratory (Professor C. E. Dent). This excluded phenyl ketonuria and the amino-acid pattern of his serum, which was also investigated by Professor C. E. Dent, was found to be normal as well. No evidence of cystinosis has been found by any of the tests applied.

He was admitted to Addenbrooke's Hospital, Cambridge, on January 11, 1957, aged 2½ years. By this time he had had further convulsions. He weighed 8.4 kg. (normal for age 16.0 kg.); his height was 75 cm. (normal 95 cm.), and his skull and chest measurements were both 44 cm. (normal 50 cm.). His fontanelle had closed. He had nystagmus, and an examination of his eyes under general anaesthesia revealed corneal opacities, but no abnormality in his lenses or fundi, and it was considered that he could distinguish light and shade, and probably also recognize shapes. He had some

TABLE 1

THE CONCENTRATION OF ELECTROLYTES AND OF CERTAIN OTHER SUBSTANCES IN THE SERUM OF THE PARENTS, THE MOTHER'S SISTER AND THE TWO CHILDREN

	Na (mEq./l.)	K (mEq./l.)	Cl (mEq./l.)	Total CO ₂ (mEq./l.)	Inorganic P (mg./100 ml.)	Creatinine (mg./100 ml.)	Urea (mg./100 ml.)	Protein (g./100 ml.)
Normal values (various sources)	130-150	4.1-5.6	98-106	22.5-32.9*	2.5 a 4.6 c	0.7-2.0	15-40	6.5-8.2
Father	139	4.4	102	28.4	—	1.2	30	—
Mother	140	4.3	105	25.7	3.6	0.9	24	—
Maternal aunt	150	4.1	107	23.4	—	1.6	24	—
Older child (M)	132	6.5	109	13.7	4.9	1.5	112	7.7
Younger child (C)	130	7.6	110	11.7	8.4	—	100	6.1

* Unpublished data from J. R. Elkinton's laboratory based on 142 determinations in 50 subjects.

a = adults.

c = children.

TABLE 2

ACID-BASE RELATIONSHIPS IN THE URINE OF NORMAL ADULTS AND BABIES, THE PARENTS, THE MOTHER'S SISTER, THE TWO PATIENTS, AND ADULTS AND CHILDREN WITH TYPICAL RENAL ACIDOSIS

	On normal diet					After 5 days ammonium chloride				
	pH	Titrateable acidity (TA) (mEq./24hr.)	Ammonia (mEq./24hr.)	NH ₃ × 100 TA + NH ₃	Inorganic P (mg./24hr.)	pH	Titrateable acidity (TA) (mEq./24hr.)	Ammonia (mEq./24hr.)	NH ₃ × 100 TA + NH ₃	Inorganic P (mg./24hr.)
Mean of 7 normal adults	5.9	26.0	23.0	47.0	799	4.6	47.0	84.0	66	984
Range	5.5	30.0	33.4	39-56	1,140	5.0	63.0	154.0	58-74	1,680
Father	5.5	26.3	35.0	52.9	790	5.0	57.0	180.0	71	1,250
Mother	5.8	26.3	24.0	57.0	—	4.7	42.0	85.0	76	—
Maternal aunt	5.8	31.0	24.0	43.5	—	4.7	42.0	85.0	67	—
Normal babies (age 10 months)	6.3	4.8	5.9	55.0	141	5.4	7.0	12.4	64	142
Older child (M)	4.9	7.4	2.9	28.0	228	—	—	—	—	—
Renal acidosis										
Adults (mean of 3)	6.4	12.1	23.2	66.7	—	5.8	27.2	47.8	65	—
Children (mean of 6) (Latner and Burnard, 1950)	6.5	2.2*	5.2*	70.0	10†	—	—	—	—	—

* m. mols./2 hr.

† mg./2 hr.

intention tremor and a flexor plantar response. He was unable to sit up unsupported, and his mental achievements were those of a child of 6 mths. His blood pressure by auscultation was found to be 95/60. His blood count was quite normal and remained so for the next year. He was examined radiologically with great care by Dr. F. R. Berridge, but nothing characteristic or diagnostic was found.

M. was treated for some time with enough sodium and potassium citrates to raise the total CO₂ in his plasma to about 23 mEq./l. At this level of plasma CO₂ he sometimes passed an alkaline urine (Schwartz, Hall, Hays and Reiman, 1959), but his blood urea remained raised to between 80-100 mg./100 ml., and clinically he did not materially improve. He was discharged on March 7, 1957, readmitted April 5—June 27, again for a few weeks in August-September, and finally in late January, 1958. His weight was then 9.1 kg. and his height 86 cm. His physical signs were unchanged, but he had had more vomiting with some diarrhoea and had had more fits. His blood pressure was 120/90 and his blood urea on February 21 was 124 mg./100 ml. Gastric juice was removed and found to contain 15 ml. N/10 HCl/100 ml. A lumbar puncture was performed

and normal fluid under normal pressure was removed. The amino-acid pattern of this fluid was examined by Professor C. E. Dent and no abnormalities were found. The concentration of glutamine was 7.8 mg./100 ml. Dr. J. M. Walshe, who kindly made this determination, considered the figure to be a normal one, as also was the one found for his blood ammonia.

An electro-encephalogram was recorded on February 4. It was reported upon as being very abnormal. No part of the cerebrum appeared to be functioning physiologically, and a lumbar puncture six days before could not be held responsible.

It was considered justifiable at this time to study M.'s reaction to acetazolamide. This was done while he was being treated with citrates and his plasma CO₂ was normal. Table 3 shows the results that were obtained after he had been given 188 mg. of acetazolamide/day. His urine became alkaline and the total CO₂ in his plasma fell from 30 to 16 mEq./l. The concentration of sodium in his serum fell at the same time from 138 to 127 mEq./l. It was concluded that this was the reaction of a person with a normal carbonic anhydrase mechanism in the renal tubules.

The boy was treated with 25 mg. of methyl testosterone

per day from February 14 to March 12. He improved clinically, gained some weight and became more alert, but his blood urea was 166 mg./100 ml. on the last date, and his treatment was then changed to 0.5 mg. of 9- α -fluorohydrocortisone. Three days later (March 15) he was obviously not so well, had become lethargic and had lost any inclination for food. The concentration of urea in his plasma was found to be 195 mg./100 ml. Next day his temperature had risen to 102° C., pulse to 160 and respirations to 60/min. His blood urea on March 17 was 263 mg./100 ml. and his haemoglobin was found to have fallen to 7.5 g./100 ml. He was accordingly given a transfusion of 250 ml. of whole blood followed by 100 ml. of $\frac{M}{6}$ sodium lactate since his plasma 'total CO₂' was only 13 mEq./l. He passed about 500 ml. of urine on March 15 with a specific gravity of 1008. His serum chemistry on March 19 was as follows: urea 277 mg./100 ml., Na 142, K 4.6, Cl 80 mEq./l., total CO₂ 36.5 mEq./l. By this date he was passing very little urine and he died on March 23, 1958.

TABLE 3
THE EFFECT OF ACETAZOLAMIDE ON THE SERUM AND URINE OF THE ELDER SIBLING (M)

	Before Acetazolamide	After Acetazolamide
Urine pH	6.4	7.8
Serum Na mEq./l.	138	127
K "	6.1	6.8
Cl "	100	99
CO ₂ "	30	16
Urea mg./100 ml.	153	209

Case 2 (C), the younger brother of M. was born on March 1, 1956. He weighed 3.1 kg. at birth and the circumference of his skull was 35 cm. He always took his food badly, and by 7 weeks had gained no weight. In the light of his elder brother's records he was suspected at this age of being mentally defective. After a few months he began to have attacks of vomiting. At the age of 7 months he was admitted to the Leicester Royal Infirmary. He weighed at this age 6.5 kg. He was 'floppy' and hypotonic and could not hold his head up, but his reflexes were normal. He did not appear to be blind but had corneal opacities, and did not follow a light with his eyes. His systolic blood pressure by the flush method was 70 mm. Hg; retinal vessels which could be seen were stated to be somewhat attenuated.

Samples of his blood were taken and analysed in November, 1956, and some of the results will be considered later (Table 1). Other findings in the serum at that time were calcium 9.6 mg./100 ml., and phosphatase 25.5 King Armstrong units. Samples of his urine were investigated by paper chromatography by Dr. H. Bickel on two occasions for unusual amino acids, but none were found. Several concentration tests were made and the highest specific gravity was 1017. The pH was consistently low and the lowest figure recorded was 5.0. An intravenous pyelogram was carried out, and both kidneys appeared to excrete the opaque material norm-

ally. X-ray photographs showed no signs of osteoporosis or renal calcification.

The child contracted an intercurrent infection with diarrhoea in December, 1956, but death was probably the result of functional renal failure, for his blood urea, shortly before death, was found to have risen to 186 mg./100 ml. on December 26, 1956, and the pulmonary oedema found after death was considered to be uraemic in origin.

Acid-base Records and Comparisons

Table 1 shows the findings to be expected in a normal serum, and the results which were obtained on investigating the father and mother of the two children, the mother's sister, and the two children themselves. The figures given for M are the means of several samples all taken during his first two admissions to Addenbrooke's Hospital. It will be noted that no abnormalities were found in the father, mother, or mother's sister and that both children had low concentrations of sodium in their serum, high concentrations of potassium, and very low 'total CO₂'. They also had concentrations of urea above the normal limits, but the plasma levels of inorganic phosphorus and creatinine in M were essentially normal.

Table 2 shows the averaged findings for the 24 hour urines of six normal adults before and after the administration of 2 to 2.5 mEq. of ammonium chloride per kg. per day for five days. It also shows the results for the same test on the father and mother of the two children, and on the mother's sister. Results for some normal babies and some cases of juvenile renal acidosis are included; some of these have been taken from the literature. The results for M are given in heavy type. Unfortunately those for the young child, C, are limited. It will be seen that:

(1) The average pH for the seven normal persons on their customary diet was 5.9, and the percentage of the surplus anions excreted as ammonia, i.e. the ammonia $\times$ 100/ammonia + titratable acidity was 47. This conforms with the findings of Marriott and Howland (1918), Van Slyke, Linder, Hiller, Leiter and McIntosh (1926) and of Linder (1927). In this paper the equivalent of the titratable acidity + ammonia will be referred to as the 'surplus non volatile anions', or simply 'surplus anions'; in the absence of urinary bicarbonate this is a measure of the excretion of acid or hydrogen ions.

(2) After five days on ammonium chloride the pH of the normal urines had fallen to 4.6, the titratable acidity had increased, but to a smaller extent than the ammonia, and the percentage of the surplus anions excreted as ammonium salts had risen to 64; this was in accordance with expectation (Davies and Yudkin, 1952; Rector, Seldin and Copenhaver, 1955; Ryberg, 1948).

(3) No abnormalities were detected in the father or mother.

(4) The percentage of the surplus anions excreted by the mother's sister as ammonium salts on her customary diet may have been somewhat below the normal average, but it was not below the normal range and the response to an acid load was perfectly normal.

(5) The patients with renal acidosis were unable to achieve the normal acidification of the urine but the percentage of the surplus anions excreted as ammonium salts was quite normal.

(6) Both children were able to lower the pH of their urine to the normal extent, but the percentage of the surplus anions excreted by M as ammonium salts was abnormally low. It was, moreover, consistently so. Only one figure above 30 was obtained.

Post Mortem Findings

Naked Eye Appearances. A post mortem examination was conducted in both children, but in greater detail on the older child and the account which follows is based upon findings in the latter except where the younger child (C) is specifically mentioned.

There was nothing characteristic about the external appearances of either child. No abnormality was detected in the liver, gall bladder, bile ducts, spleen, portal vein or its branches. The same applies to the oesophagus, stomach, small and large intestine. The pancreas was of normal size in M's case but rather hard and the cut surfaces were very firm; the ducts were normal. All parts of the heart were normal; there was a normal distribution of the great vessels and their branches and the renal vessels were normal. The lungs of M showed tiny areas of collapse along the posterior borders but otherwise appeared normal; the air passages were lined by dry grey mucosa; the larynx, tonsils and middle ears were normal. As already mentioned the lungs of the young child (C) were oedematous. The bones were macroscopically normal; the costo-chondral junctions, the right femur and an entire vertebral strip were inspected. The pituitary, thyroid, thymus and suprarenal glands were all normal.

The brain was highly abnormal. Small sunken areas of atrophy were present in gyri of the superior parts of the parietal lobes (Fig. 1). There was also conspicuous cerebellar atrophy. The cerebellum as a whole was

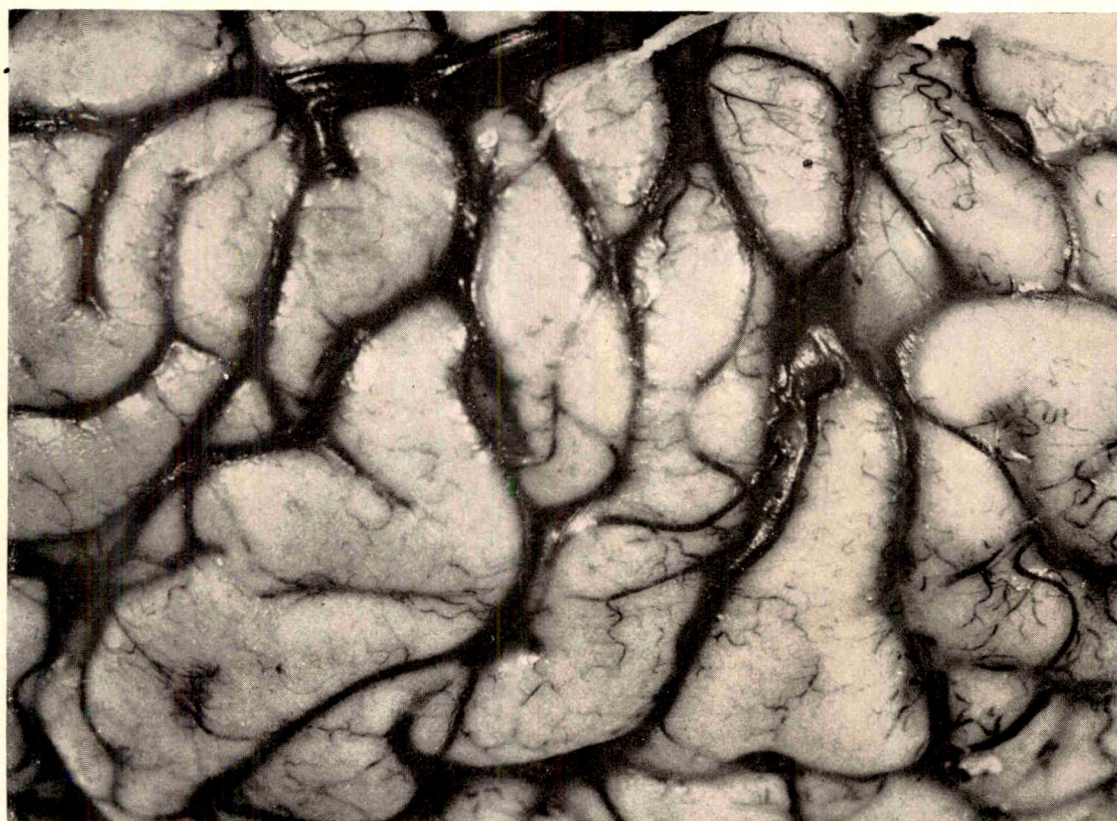


FIG. 1.—Parietal cortex of M showing a small area of atrophy.

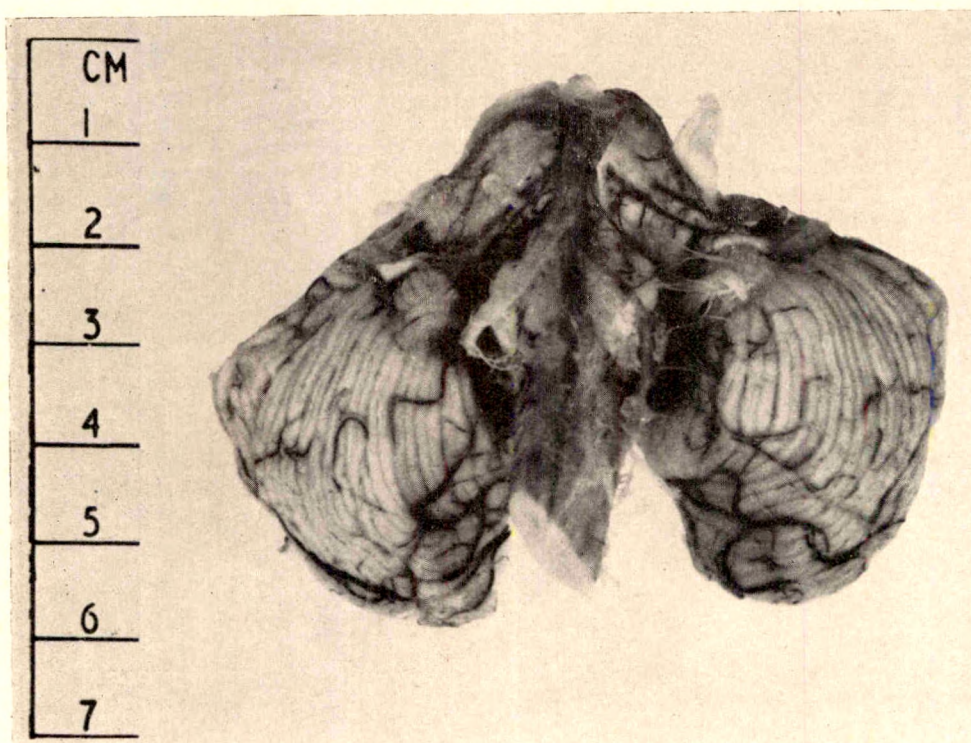


FIG. 2.—Cerebellum showing reduction of size and symmetrical areas of atrophy.

small, the folia being below the normal size and the vermis and nodule almost completely atrophic (Fig. 2). The cerebral veins and arteries were normal, however, as were the dural sinuses and meninges. No abnormality was found in the spinal cord.

Both testes were absent from the scrotum, nor could they be located in any of the usual ectopic sites; all that could be found were slight swellings on the spermatic cords near to the attachment of the gubernaculum to the scrotum. C had horseshoe kidneys but no other anatomical abnormalities. In M's case the renal cortex showed a curious yellow speckling and was of reduced width (0.2 cm.) compared with a control (0.5-0.6 cm.) of the same age. The renal pelves, ureters, bladder and penis were normal.

Histological and Enzymatic Examinations. Pieces of tissue were taken from many of M's organs and fixed in 10% formaldehyde saline. Pieces of kidney, liver, pancreas, heart and brain were 'freeze substituted' in butanol and embedded in water soluble wax; these pieces were examined histochemically for the distribution of a variety of enzymes. Portions of C's kidney were preserved at -15°C .

The kidneys of both children showed the same abnormalities to a similar degree. Deposits of calcium were visible within epithelial cells in the distal parts of the

tubules and in the loops of Henle, but the exact site was difficult to define. In M's case epithelial nuclei were outlined by rings of calcium, as they may be in the metastatic nephrocalcinosis due to acidosis or alkalosis. The glomeruli in the superficial zone of the kidneys were abnormally small. Apart from their size some were normal while in others the parietal layer of Bowman's capsule was thickened (Fig. 3a and b). No such appearance was found in controls. The renal vessels appeared normal in the sections. No other abnormality was found in the remainder of the urinary tract. Sections of the lower ends of M's spermatic cords showed the epididymis to be present but none of the sections revealed any evidence of testicular tissue. The nuclei in the skin and other tissues of the older child were chromatin negative, suggesting that the genetic sex was male.

The cerebellum showed small widely spaced folia with absence of a granular layer and the presence of numerous Purkinje cells, many of them within the molecular layer (Fig. 4). All contained abundant protein when stained by the tetrazo method (Fig. 5); gliosis was scanty in the granular layer. The pons, olives, dorsal and ventral spinocerebellar tracts were normal and so were the dentate nuclei. Sections of the cerebral hemispheres revealed a deficiency of neurones in the areas of microgyria but no other abnormality was found in sections from most parts of the brain and cord. The right eye

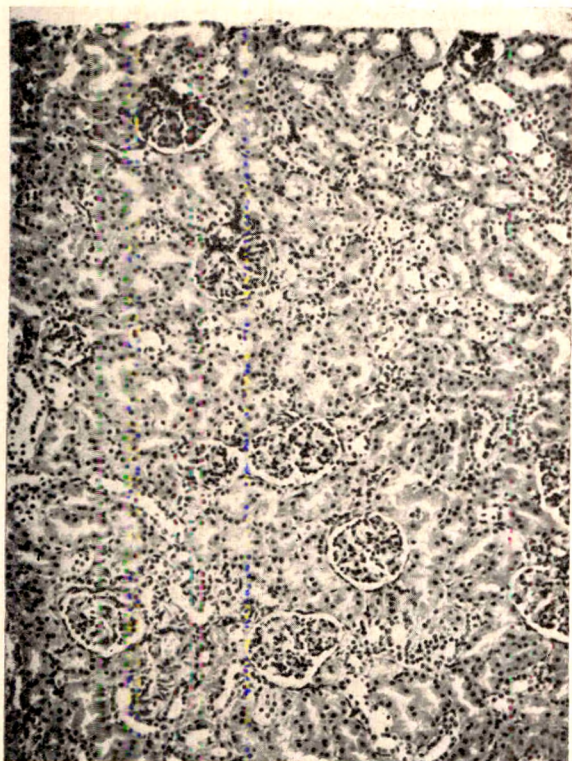


FIG. 3a.

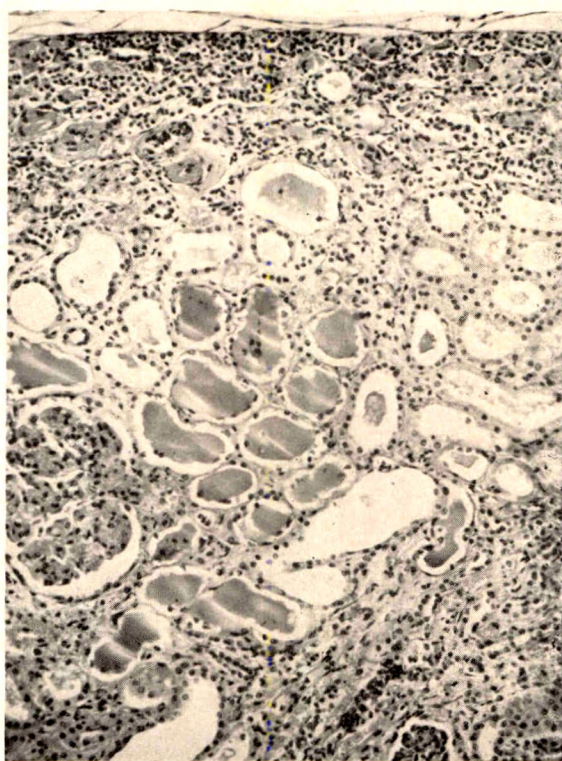


FIG. 3b.

FIG. 3a.—Section of a normal kidney from a child of the same age as M. (H and E $\times 115$)

FIG. 3b.—Section of M.'s kidney showing a superficial zone of small fibrotic glomeruli and enlargement of an adjacent nephron. (H and E $\times 115$)

FIG. 4.—Section of M.'s cerebellar cortex. Note the absence of the granular layer and the necrotic Purkinje cells near the surface. (H and E $\times 115$)

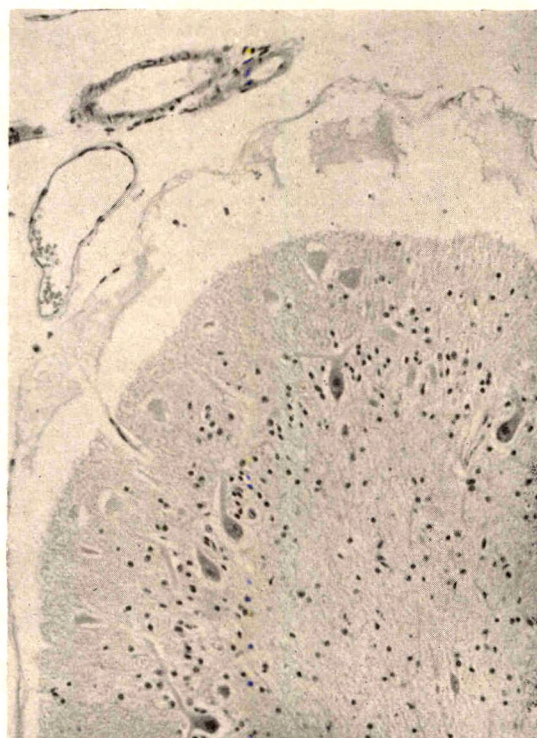


FIG. 4.

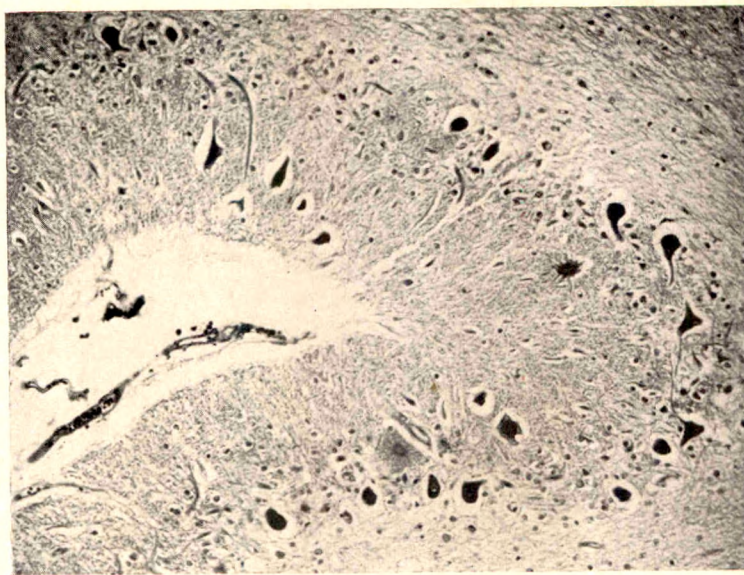


FIG. 5.—Asteroïd structures in the cerebellar cortex. Abundant protein is present in both normal and dead Purkinje cells. (Tetrazo method for protein, $\times 115$)

was examined and some early corneal keratinization and vascularization were found but no other abnormality. These appearances in the cornea were similar to those which had been found in the cornea of the younger child C.

Premature ossification was a feature in the columns of cartilage of the epiphyseal plates at the upper end of the femur (Fig. 6) (Harris, 1933).

No abnormalities were found during the histological examinations of various parts of the gut, and plasma cells were seen in moderate numbers in the lamina propria mucosae of the intestine.

All the lobes of M's lungs contained histological abnormalities: some of the veins had agonal thrombi in them, and many of the bronchioles and alveolar ducts contained vegetable debris, indicating that some of the stomach contents had been inhaled just before death and the occasional presence of foreign body giant cells suggested that inhalation of vomit had occurred previously.

Histochemical examinations of freeze substituted pieces of M's kidney, liver, pancreas and brain were made. Acid and alkaline phosphatases and non-specific

esterases were studied, but the only significant abnormality was the presence of acid phosphatase activity near to the deposits of calcium in the kidneys. An overall reduction of esterase activity was found in C's kidney associated with some spots of intense activity in certain cells. Portions of C's kidney were examined many months after the child's death for their glutaminase activity and the values found, which are given in Table 4, must be considered normal.

Discussion

The Differential Diagnosis.

There is nothing really diagnostic about a disinclination for food and a failure to thrive which were the earliest causes of anxiety. Recognition of the mental retardation, corneal opacities, nystagmus and photophobia came later, as did the severe reduction in the plasma bicarbonate, and

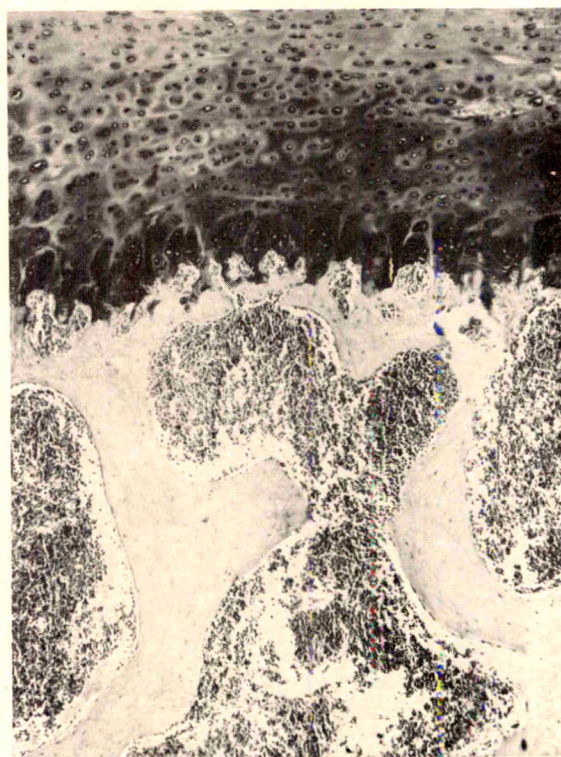


FIG. 6.—Section of M's upper femoral epiphyseal plate to show the arrest of growth. (H and E $\times 45$)

TABLE 4

THE GLUTAMINASE ACTIVITY OF THE KIDNEY OF THE YOUNGER CHILD AND OF A CONTROL OF ABOUT THE SAME WEIGHT

(see Radde and McCance, 1959)

	mg. NH_3 /100 mg. dry matter/hour	
	Patient	Control
Without added glutamine	103	84
With added glutamine	353	215

the raised blood urea. The highly acid urines, however, separate M and C from the children described by Lowe *et al.* (1952), and by Royer and Prader (1957) because all of the latter were apparently unable to acidify the urine and therefore were correctly diagnosed as cases of renal tubular acidosis (Stapleton, 1949; Doxiadis, 1952; Wilkinson, 1954). They were also excreting large amounts of organic—probably amino acids—in their urine (Jackson and Linder, 1953; Piel, 1957; Jonxis, 1957; Mudge, 1958). The present children were not, and the amino acid patterns of the serum and C.S.F. of the elder boy (the only one whose C.S.F. was tested) were also normal. These findings were taken at the time to rule out cystinosis, and this was again excluded by chemical and histochemical tests made on the tissues after death. Other records which were studied in making the differential diagnosis were those of Goldbloom *et al.* (1957). The disease in their cases had a different age of onset, and the patients suffered from nerve-deafness and a lesion described as chronic interstitial pyelonephritis. These syndromes, like the present one, may be familial (Cooke and Kleeman, 1950; Rendle-Short, 1953; Schreiner, Smith and Kyle, 1953; Foss, Perry and Wood, 1956; Wrong and Davies, 1959).

It is frequently stated that patients with renal tubular acidosis are unable to excrete ammonia (Lowe *et al.*, 1952; Lowe and Smith, 1955; Albright, Burnett, Parson, Reifenstein and Roos, 1946; Albright, Consolazio, Coombs, Sulkowitch and Talbot, 1940; Baines, Barclay and Cooke, 1945; Boyd and Stearns, 1942; McCune and Pray, 1940; Piel, 1957; Debré *et al.*, 1955; Debré, Royer and Lestrade, 1956; Royer and Prader, 1957). Some authors have considered that there is no real interference with the formation of ammonia in this disease (Gabrielsen, 1954; Stapleton, 1949; Latner and Burnard, 1950; Wrong and Davies, 1959). With this the information given in the literature is really in agreement (see Table 2), although the patients may have been said to be unable to excrete ammonia. The patients of Lowe *et al.* (1952), for example, had perfectly normal $\text{NH}_3/\text{NH}_3 + \text{titratable acidity}$ ratios in their urine; the figures given averaged over 0.6, and there is no evidence that their kidneys could not have produced NH_3 in normal measure if there had been any way of putting them under test by making the urine acid. There is nothing in renal tubular acidosis comparable to the findings in these two children in whose urines the ammonia formed less than 30% of the ammonia + the titratable acidity even when the pH had been very low for weeks. This is the state of affairs

originally described by Palmer and Henderson (1915) and Henderson and Palmer (1915), who reported that, in some patients with advanced chronic glomerular nephritis, the $\text{NH}_3/\text{NH}_3 + \text{titratable acidity}$ ratios were subnormal. These findings have been confirmed by several investigators and the whole subject brought up to date by Schwartz *et al.* (1959) and by Wrong and Davies (1959). M was investigated when the concentration of urea in his plasma was still only 100 mg./100 ml. or less, and his concentrating power reasonably good. The kidneys of both children were examined after death and neither of them had lesions in any way resembling chronic glomerular nephritis as had those of the children with a somewhat similar syndrome reported by Goldbloom *et al.* (1957). It was concluded therefore that a feature of our cases was a rather specific failure of the kidney to excrete ammonium ions—see Wrong and Davies (1959). Talbot, Sobel, McArthur and Crawford (1952) have described one patient who appears to have had a specific renal deficiency in the excretion of ammonia, but no others seem to have been recorded. Talbot *et al.* (1952) were interested in such patients mainly because the lesion might lead to the excretion of so much fixed base, particularly of calcium, that the patients developed osteomalacia. They therefore described their case in the section of their book dealing with the parathyroid glands, and the authors have informed us that contact with this patient has been lost.

The Normality of the Titratable Acidity. The excretion of a subnormal percentage of the total surplus anions as ammonium salts might have been caused by a very high titratable acidity in the urine due to the excretion of abnormal buffer substances. There was no evidence of this in M or C, for the amino acids in the urine were normal in amount and type, and the quantities of phosphates excreted in the urine were enough to account for the customary percentage of the titratable acidity. Thus the average percentage for six normal adults was 65 after five days on ammonium chloride and M's average over three days, before being treated, was 75%. The pH of the urines both in the adults and in M ranged from 4.6–4.9. There is no evidence, therefore, that the titratable acidity was unusually magnified in quantity or form or that the $\text{NH}_3 \times 100/\text{NH}_3 + \text{titratable acidity}$ was abnormal for this reason.

The Ammonia Coefficient. M's failure to excrete ammonia suggested an investigation of the percentage of his total nitrogen excreted as ammonium

salts (the ammonia coefficient). This was very low, particularly when the pH of the urine was taken into account. Thus, out of a group of eight urines all with pH between 4.6 and 4.9, M's ammonia coefficient averaged only 1.6. The ammonia coefficient of the six normal adults averaged 3.5 when their urines had an average pH of 6.0, and the ammonia coefficient rose to 11.5 after five days on ammonium chloride.

The Nature of the Lesion. The lesions as a whole should probably be regarded as developmental failures, but the cerebral and cerebellar findings are unusual. Agenesis of the cerebral and cerebellar cortices usually leads to degeneration of the Purkinje and granular cells and extensive atrophy of the cerebral cortex (Norman, 1958). Furthermore the vermis and flocculi are usually normal, which they certainly were not in this case (Fig. 2). The cortical and cerebellar lesions appear not to have been neurologically associated since the pontine and dentate nuclei were normal, and no abnormality was detected in the cerebral peduncles or in the thalamus.

The cerebellar lesion is probably best considered as a developmental failure or early atrophy of cells in the granular layer, and if this is so the conspicuous involvement of the vermis is unusual (Ule, 1952). The suggestion is supported however by the asteroid like brushwork of fibres derived from Purkinje cells (Fig. 5); and another finding in favour is that the inferior olives were normal. The aetiology of cerebellar granular atrophy is in some cases familial (Norman, 1940) and usually associated with severe mental defect, as it was in this boy.

Both testes were absent and the case might, therefore, be classified as belonging to Klinefelter's syndrome in which mental abnormality, feeble-mindedness and idiocy have been described by Ferguson-Smith (1958). Total absence of both testes is a decidedly rare anomaly. The finding of chromatin positive (Barr positive) nuclei neither supports nor refutes a diagnosis of Klinefelter's disease.

The other conspicuous abnormality lay in the kidneys, where the thin rind of small cortical glomeruli again suggests development failure, though it is just possible that some of the appearances might have been the result of pyelonephritis. The deposits of calcium and the occasional paratubular granulomata were probably sequelae of the metabolic disturbances which were such a feature during life. The high concentration of urea in the serum of both children indicates that their glomerular filtration rates were low. Determinations of M's endo-

genous creatinine clearance were found to be 0.7 ml./kg./min. on December 17, 1957. Some lowering of the glomerular filtration rate in the absence of much, if any, histological sign of glomerular destruction is also in keeping with the large numbers of small and apparently undeveloped glomeruli in the peripheral parts of the cortex. It is just possible that the failure to excrete ammonium was functionally connected with these low glomerular filtration rates and not with any tubular lesion (Wrong and Davies, 1959), but M's glomerular filtration rates were not low enough in the early stages of his disease for this to be a very satisfactory explanation.

Summary

The following syndrome has been defined following its investigation in two brothers whose parents were unrelated and healthy.

Little desire for food from birth; failure to grow and thrive; later, vomiting and sporadic attacks of diarrhoea.

Corneal opacities, partial blindness and nystagmus.

Mental retardation, intention tremor and (in one sibling) convulsions.

Serum: 'total CO₂' very low, sodium low normal, potassium over normal, phosphorus normal, urea in the early stages 80-100 mg./100 ml., terminal stages 270 mg.

Urine: always sterile, highly acid. Sp. gr. 1017 or more in the early stages. $\text{NH}_3 \times 100 / \text{NH}_3 + \text{titratable acidity}$ abnormally low, but no reduction in the glutaminase activity of the kidney *in vitro*.

Normal response to acetazolamide (one test).

Death from progressive renal failure.

Post mortem: conspicuous structural abnormalities in the brain, slight keratinization and vascularity of the cornea. Some calcification of the kidney. Many small (perhaps undeveloped) glomeruli in the periphery of a narrow cortex and no testes.

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SIRENOMELIA AND MONOMELIA WITH RENAL AGENESIS AND AMNION NODOSUM

BY

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Interest has recently been directed towards symphodia, a foetal malformation better known by the synonyms sirenomelia, symphus dipus or mermaid foetus. This malformation consists of more or less complete fusion of the lower limbs to form a single extremity.

Less frequently reported is the condition described by Ballantyne (1904) as monopodia, in which there is a single lower extremity which shows no indication that it has been derived from the fusion of two lower limbs. For this abnormality we prefer the term monomelia.

Severe dysplasia of the foetal urinary tract is apparently an invariable accompaniment of sirenomelia and monomelia. Despite the considerable number of cases described in the literature scant attention has been paid to certain other associated features in the foetus. Only occasionally is reference made to the liquor amnii, and there are no previous histological studies of the placental membranes.

Case Reports

Case 1. The mother, aged 35, para. 9, gravida 10, was perfectly well throughout her pregnancy. She was uncooperative and refused ante-natal care. At 41 weeks she went into spontaneous labour and was delivered of a male foetus weighing 1,804 g. as a breech presentation. No doctor was present and consequently no observations were made as regards the liquor amnii. There was no history of the membranes ever having ruptured.

There was no consanguinity of the parents, nor maternal illness during the antepartum period.

AUTOPSY FINDINGS. The foetus showed a single midline lower extremity measuring approximately 16 cm. which terminated in a stump with no attached digits (Fig. 1). The face presented the characteristics usually associated with renal agenesis; the ears were large, flattened and low set; the nose flattened at the tip; the space between the eyes increased; the chin receding and the epicanthic folds prominent (Potter facies). The right hand was large, clumsy and spade-like; the left

had only two digits. The anus was imperforate. There were no external genitalia.

The only abnormalities noted on internal examination were small hypoplastic lungs and total absence of both kidneys. Two testes were found in the pelvis.

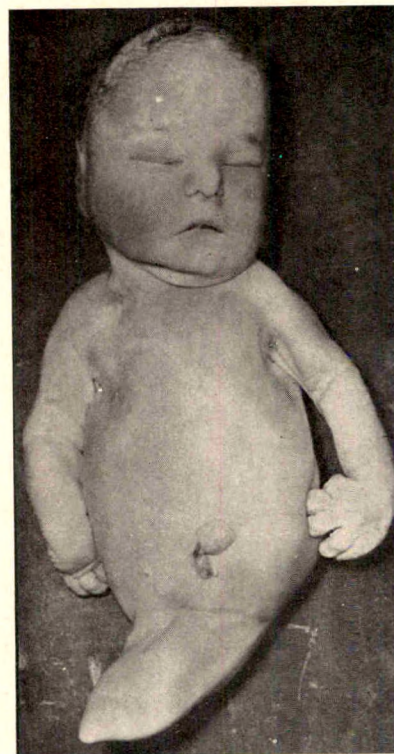


FIG. 1.—Case 1. Monomelic foetus showing large spade-like hands.

Case 2. The mother, aged 19, para 0, was perfectly well throughout her pregnancy. Although there was no doubt as to the date of her last menstrual period the uterus was found to be consistently small for the estimated period of gestation. At the forty-second week of her

pregnancy she went into spontaneous labour and was delivered of a stillborn male foetus, weighing 1,850 g., as a breech presentation. The membranes were intact up to the time of delivery and no escape of liquor was noticed.

There was no consanguinity of the parents, nor any history of maternal illness during pregnancy.

AUTOPSY FINDINGS. The foetus showed features identical with Case 1, with a single lower extremity, Potter facies, large spade-like hands, absence of external genitalia and anal atresia.

Internal examination showed that the kidneys were absent and the lungs typically hypoplastic. Two testes were found in the pelvis.

Case 3. The clinical case records could not be traced and consequently no maternal history was available.

AUTOPSY FINDINGS. The foetus weighed 1,200 g. and presented the typical deformity of sirenomelia, there being a single fused lower limb terminating in a foot on which there were two great toes (Fig. 2). The foetus



FIG. 2.—Case 3. Sirenomelic foetus with exomphalos.

showed the Potter facies, large spade-like hands, imperforate anus and no external genitalia.

There was a large exomphalos which contained the greater part of the abdominal viscera. The kidneys were absent and the internal genitalia could not be found. The lungs were hypoplastic.

Case 4. The mother was a primigravida who had excessive vomiting during early pregnancy. The uterus was found to be consistently small for the period of gestation. At 34 weeks she had an episode of vaginal bleeding and about this time also developed ankle oedema. At 44 weeks she went into spontaneous labour and was delivered of a female foetus as a vertex L.O.A.

weighing 2,300 g. The membranes were intact up to the time of delivery, and no escape of liquor was noticed.

There was no consanguinity of the parents. The only previous maternal illness was tuberculosis of the bones during childhood.

AUTOPSY FINDINGS. The foetus was a typical example of sirenomelia, with a single lower limb composed of elements of two fused limbs. The foetus showed the typical Potter facies, and the hands were large and spade-like (Fig. 3). There were no external genitalia and the anus was imperforate.

Internal examination revealed small hypoplastic lungs, complete absence of both kidneys, an enterogenous cyst



FIG. 3.—Case 4. Sirenomelic foetus showing Potter facies and large spade-like hands.

on the posterior abdominal wall, normal fallopian tubes and ovaries and a vestigial uterus but no vagina.

Placental Examination

Case 1. The placenta weighed 350 g. The foetal surface and membranes were found to be studded with numerous small whitish nodules approximately 1-2 mm. in diameter. These were firmly adherent to the amnion and presented the appearance typical of amnion nodosum. The maternal surface of the placenta showed no abnormality. The umbilical cord contained three vessels.

Microscopical examination of the membranes confirmed the presence of amnion nodosum typified by aggregations of epidermal squames embedded on the surface of the amnion. The placental tissue itself was normal.

Cases 2 and 3. No note was made in the macroscopical examination of any abnormal appearance of the amnion. Retrospective microscopical examination of sections of the membranes revealed the characteristic lesion of amnion nodosum.

Case 4. The placenta was not submitted for examination.

Radiological Report

Radiological examination of the monomelic fetuses (Cases 1 and 2) revealed the single lower limb to consist of a femur and part of a tibia (Fig. 4).

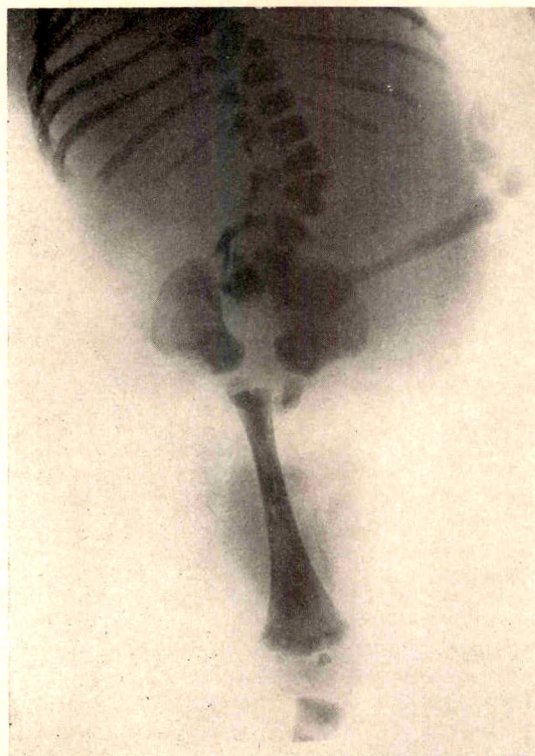


FIG. 4.—Radiograph of monomelic fetus showing lower extremity to be composed of a femur and part of a tibia.

The other abnormalities included hemivertebrae of the dorsal spine.

In the sirenomelic fetuses (Cases 3 and 4) there was fusion of the lower limbs with two femora and two deformed tibia (Fig. 5). No fibulae were

present, but there were irregular areas of ossification in the site usually occupied by these bones. There were no tarsal bones but a 'bifid' single foot with irregular metatarsal and phalangeal bones.

Discussion

Babies born with either sirenomelia or monomelia are either stillborn or survive only a few hours. This fact was noted by Ballantyne (1904) and, although he was not clear as to the cause, he suggested that early death might be associated with the frequent absence of kidneys.

In the present series of cases kidneys were entirely absent, and the pulmonary hypoplasia associated with renal agenesis was a constant feature. Kidneys were, however, noted in a report by Hendry and Kohler (1956), but it is interesting that there was in this case a complete atresia of the urethra.



FIG. 5.—Radiograph of sirenomelic fetus demonstrating fusion of the two lower limbs.

The excellent illustrations of sirenomelia and monomelia by Ballantyne (1904), Foulkes and McMurray (1954), Hendry and Kohler (1956) and Jolly and Lamont (1958) show what is now regarded as the characteristic facial appearance first described

by Potter (1946a and b) in association with renal agenesis. The illustrations of these authors also show the large flattened and clumsy appearance of the hands described by Bain and Scott (1960) in connexion with severe urinary tract dysplasia. Although such features have not been generally recognized as associated with sirenomelia and monomelia, Fritzsche (1955) noted the presence of Potter facies in a case of monomelia.

References to the volume of liquor amnii are generally vague and there appears to be no definite observation of oligohydramnios. Obstetrical histories were obtained in three of the present four cases. The salient points in these histories were a uterus smaller than usual for the expected period of gestation, membranes intact until the time of delivery, and no note of the escape of liquor amnii.

These facts are highly suggestive of oligohydramnios, but proof of the absence of liquor was obtained by placental examination. In three out of the four cases the placentae were examined histologically and amnion nodosum was found to be present. As shown by Scott and Bain (1958) this lesion, which consists of plaques of epithelial squames on the surface of the amnion, is found only in association with oligohydramnios.

It is of interest that Resnick (1945) noted that hydramnios, usually expected in the presence of foetal malformations, was not present in association with sirenomelia. He quotes a case described by Bauereisen (1905). This was a twin pregnancy in association with hydramnios, one of the twins being a true symphodia and the other having anal atresia but showing absence of only one kidney. It is highly probable that the hydramnios was in fact limited to the foetus with anal atresia.

Two out of the four present foetuses were delivered as breech presentations. This abnormal presentation, frequently noted in previously reported cases, is known to be favoured by the absence of foetal micturition.

Little is known as regards the aetiology of sirenomelia or monomelia, but several theories have been put forward including the suggestion that oligohydramnios is one of the causes. The oligohydramnios is obviously secondary to an embryonic defect involving the foetal kidneys or urinary tract, and although it can account for the appearances

produced in the face and hands, it is unlikely to produce fusion of the lower limbs or monomelia. Absence of one umbilical artery has been cited as an aetiological factor on the assumption that it impairs blood supply to the lower limbs. However, absence of one umbilical artery is seen frequently in babies with varied congenital malformations and occasionally in apparently normal infants. The cause of these malformations could be either genetic damage or injury to the developing embryo by factors as yet unknown.

Summary

Two cases of sirenomelia and two of monomelia have been described in view of additional features not mentioned in previous reports. The Potter facies, large spade-like hands and pulmonary hypoplasia were present in all four cases. Examination of the placentae in three cases revealed the lesion of amnion nodosum, a finding indicative of oligohydramnios. Oligohydramnios was in fact noted clinically in two instances.

We conclude that severe urinary tract dysplasia, such as renal agenesis or complete urethral atresia, and its associated foetal and placental changes are a constant finding in sirenomelia and monomelia.

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The photography was done by Miss C. Brydon.

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THE ASSOCIATION OF SIRENOMELIA WITH POTTER'S SYNDROME

BY

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The Greeks considered congenital deformities to be of divine origin and eventually these monsters were thought to indicate a divine warning of some future calamity and the infant and even the mother were sacrificed to propitiate the gods (Glenister, 1957). The sympodial deformity has been recognized from earliest times and may well have given

rise to the myth of the siren. The legendary monster of the Lybian desert, the sciapod, or shadow foot, described by both Herodotus and Pliny (Fig. 1), may well have had a similar origin. This man used his foot as a sunshade when resting. Early writers showed a remarkable degree of wishful thinking and poetic licence in their descriptions of



FIG. 1.—The sciapod or shadow foot. This carving from a fourteenth century bench end in the nave of Dennington Church, Suffolk, shows a fused lower limb and a large foot with 10 toes. Unlike the true sympodial limb, the knees flex posteriorly.



FIG. 2.—The sympodial foetus described and illustrated by Thomas Bartholin. Note the presence of mammary glands and webbed hands.

the symphydial monster. Bartholin (1654) even reported mammary glands and webbed fingers in his case (Fig. 2).

Although the symphydial deformity is a rare condition a number of cases have been reported in the literature, and the subject has been reviewed by Kampmeier (1927) and Hendry and Kohler (1956).

The case described in this report shows the association of the abnormality with the syndrome described by Potter (1946) of renal agenesis, hypoplasia of the lungs and a typical facies. This association does not seem to have been reported in any of the cases of symphydia described up to the present, although it is probable that the association is common.

The anatomical and embryological aspects of this case have been described elsewhere (Bearn, 1960).

Case Record

A symphydial foetus, stillborn, and fixed in formalin, was made available for study.



FIG. 3.—The symphydial foetus showing the fused lower limb, with 10 toes, the two little toes fused and big toes on outer sides of foot.



FIG. 4.—The face of the symphydial foetus showing the features typical of Potter's syndrome.

Obstetric History. The mother was married, aged 22 years and had given birth two years previously to a normal 40 week infant, which had died before the arrival of the midwife. During the second pregnancy, there was no history of any abnormality and no history of oligohydramnios was reported. Labour was at 40 weeks and was uneventful, lasting six hours. She was group O, Rhesus positive. After the birth of the abnormal child, the blood of both the mother and father was again checked, and no ABO or other incompatibility was found.

External Examination. The specimen (Fig. 3) was a human foetus of indeterminate sex, with a 2nd degree symphydial deformity, weighing 2lb. 1oz.

The face (Fig. 4) showed all the features first described by Potter (1946) in association with bilateral renal agenesis: flattening of the nose, recession of the chin, soft flat ears, with apparent absence of the cartilage, and low positioning of the ears on the side of the head. The eyes showed a wide intra-ocular distance, and prominent epicanthic folds, forming a wide semicircle on each side of the nose and covering each medial palpebral commissure.

The upper limbs and thorax were normal. The pelvis was reduced in size and no external genitalia could be

found. There was a blind pit dorsally at the lower end of the trunk which could have represented an imperforate anus, otherwise no sign of an opening of the anus or urethra could be found.

The lower limbs were joined together, the site of the fusion being along the post-axial borders of the limbs as far as the tips of the little toes. The soles of the feet faced anteriorly. Ten toes were present, the two outermost toes being the big toes, and the two little toes being partially fused together in the midline. The two patellae were felt on the postero-lateral aspect of the knee, and the joint could be flexed anteriorly.



FIG. 5.—Radiograph showing the double skeleton of the single limb, with the fibulae lying internal to the tibiae.

Radiological Examination of the Lower Limb. The radiograph showed no abnormalities in the upper limbs, head and trunk (Fig. 5). Six lumbar vertebrae and the first two pieces of the sacrum were present, the remaining three pieces and the coccyx being absent. The ilium was present on each side, and the pubis was represented by a fused midline bone. The radiograph of the fused limb showed the presence of both femora, and both tibiae and fibulae, their relative positions being reversed. Two tarsal bones, and the metacarpals and phalanges, were present.

Internal Examination. The internal structures of the head and neck were normal. The heart was normal,

but the lungs were markedly underdeveloped and failed to fill the thoracic cavity, this hypoplasia being more marked on the left side, and the pleural cavities were filled with fluid. The size of the thoracic cavity was normal. The alimentary tract was normal as far as the rectum, which ended as a blind stump. The liver, spleen and pancreas were normal, the left adrenal only was present, and was flattened antero-posteriorly and the kidneys and ureters were absent except for a small mass on the left side below the adrenal gland, which was shown histologically to contain some renal tissue. The pelvic cavity was very shallow and contained none of its normal contents. The urogenital tract was absent and the external genitalia could not be found. The testes were present in each iliac fossa. Only the right umbilical artery was found.

The Skeleton and Musculature of the Pelvis and Lower Limb. The main muscle groups of the pelvis and the fused limb were all present and with very few exceptions, even the individual muscles of each group could be identified. The muscles of the gluteal region were present and were in their normal positions, the greater trochanters being in a more posterior position than usual. These two regions were in much the same relative positions as in the normal foetus. The upper two-thirds of the thigh showed only a partial reversal from the normal position, and each patella was identified on the postero-lateral aspect of the thigh. From the knee joints downwards, the limbs showed a complete reversal of position, and flexion of the knee joint was in an anterior direction. The tibia and fibula on each side were reversed, the two fibulae being adjacent to each other on the internal aspects of the tibiae. The femoral, obturator and sciatic nerves were identified in each limb supplying their respective muscle groups. The details of the muscles and skeleton have been reported in an earlier paper (Bearn, 1960).

Discussion

The condition of symphyal foetus is most uncommon. Ballantyne (1898) collected only 120 cases in the literature; Kampmeier (1927) collected 51 more cases, including one of his own. Since then occasional reports of individual cases have appeared in the literature: Dreyfuss (1928), Newbill (1941), Resnick (1945), Dodek and Friedman (1950), Potter (1952), Foulkes and McMurray (1954), Jones and Lee (1955), Hendry and Kohler (1956), Jolly and Lamont (1958).

Symphyal foetuses are classified into three degrees, depending on the completeness of the fusion of the two limbs, Förster (1861, 1865).

- (1) **Symelia apus.** No feet are present, the limbs are completely fused into one single limb. One femur and one tibia are present.
- (2) **Symelia unipus.** One foot is present, this being a partial fusion of the two feet. Up to

ten toes may be found, the little toes being fused together and the plantar surface of the foot facing anteriorly. Two femora and two tibiae and fibulae are present, the latter bone being medial to each tibia. The main muscle groups can usually be identified.

- (3) **Symelia bipus.** Two feet are present, giving the appearance of fins—hence the name 'mermaid' foetuses for this abnormality. The fusion of the limbs extends only as far as the ankles, and the muscles of the two limbs are all present.

The position of the fused limb in this condition is of great embryological interest, as it demonstrates a persistence of the early foetal unrotated position of the limb. The normal lower limb undergoes internal rotation, so that the post-axial border and digit of the little toe become lateral and the ventral surface faces posteriorly. In the sympodial deformity the developing limb buds are fused from the start along their post-axial borders and rotation is therefore impossible.

Causation of the Sympodial Deformity. This has been discussed in detail elsewhere (Bearn, 1960). Bolk (1899) and Ballantyne (1904) both suggested that the defect was primarily a failure of development of the caudal segments at a very early stage before the limb buds form. Wolff (1936) has produced the sympodial deformity in the chick by destroying the caudal end of the early embryo with x-rays. This work of Wolff (1936) confirms experimentally the suggestions that the primary defect in the sympodial deformity is one of the caudal region of the embryo, but how this defect is produced in the early human embryo is not known. The defect must also involve the presumptive area for the urogenital tract, as these structures including the kidney do not develop in the human monster.

The Association of Sympodia with Potter's Syndrome. The face of this foetus (Fig. 4) shows all the characteristics, first described by Potter (1946), found in cases of renal agenesis. 'The most striking feature consists of an increase in width between the eyes and the presence of an unusually prominent fold arising at the inner canthus of each eye. The fold sweeps downward and laterally to form a wide semicircle under the inferior medial aspect of each orbital space. Other changes . . . are a flattening and slight broadening of the nose, an unusually receding chin and large low-set ears which have proportionately little cartilage.' Although this facies has not been reported in any of

the papers on sympodia published since Potter's paper in 1946, it is likely that most sympodial foetuses show these features, in view of the usual absence of renal tissue in this deformity. In the paper by Hendry and Kohler (1956) Fig. 6 shows some of the features of this facies, and in the paper by Jolly and Lamont (1958) Fig. 1 shows most of the characteristics, including the epicanthic fold. However, the specimen described by Jones and Lee (1955), now preserved in the Anatomy Department of the Middlesex Hospital Medical School, shows a normal facies in spite of complete absence of renal tissue. Hilson (1957) has shown that abnormalities of the ears, somewhat similar to those seen in Potter's syndrome, occur in other malformations of the urinary tract, such as bifid ureter, or absence of one kidney.

It is not yet possible to explain the association of the typical facies described by Potter (1946) occurring in renal agenesis and in cases of sympodia.

It is possible that the peculiar facies may be explained by the compression of the head by the uterine wall, secondary to the oligohydramnios which is usually present both in sympodia and in cases of renal agenesis without gross abnormalities of the lower limbs.

The flattening of the nose, the receding chin and the flattened malpositioned ears could all be due to a mechanical pressure effect on the developing head.

The presence of oligohydramnios was not reported in the obstetric history of this patient, although it is often noticed in both sympodia and renal agenesis, and it is probable that there is a direct relation between the renal agenesis and the oligohydramnios. Browne (1955) believes that oligohydramnios with compression of the foetus is a factor in the development of club foot deformity. For example, Davidson and Ross (1954) described six cases of Potter's syndrome, all of which had club foot. Although mechanical pressure of the uterus may well explain the club foot deformity associated with renal agenesis and oligohydramnios, there are no grounds for believing that the gross deformity of sympodia could be a consequence of these conditions.

Potter (1946) also described for the first time the hypoplasia of the lungs which occurs in renal agenesis. This foetus showed the hypoplasia to a marked degree, the left lung filling only a fraction of the cavity. Again, recent reports on sympodia do not discuss this point, although Jolly and Lamont remark that the lungs in their case 'were poorly expanded'. It is again likely that the examination of most cases of sympodia with this point in view would reveal the abnormality. It is not possible to explain the failure of development of the lungs on

mechanical grounds, as the thoracic cavity was normal in size. The reason for the hypoplasia remains obscure.

The absence of the kidneys explains the large flattened appearance of the adrenal gland found in this case and reported in most cases of sympodia, and also by Potter (1946) in her cases of renal agenesis. The development of the kidneys presumably moulds the adrenals into their characteristic shape in the normal foetus.

The observation that all sympodial monsters have but one umbilical artery is a curious finding. In this case it was the right umbilical artery which persisted, although both Ballantyne (1904) and Kampmeier (1927) found, in their cases, that the artery within the umbilical cord was a persistent vitelline artery.

The sex of this foetus is male, and all collected series show a predominance of this sex. Kampmeier (1927) found 38 males out of a series of 52 sympodial monsters, and Potter (1952), in her series of renal agenesis, found a majority of males, only four out of 26 being female.

Summary

A case of sympodia is described, showing a second degree deformity (Symelia unipus).

The association of this deformity with Potter's syndrome, the typical facies, aplasia of the lungs and renal agenesis, is described.

I am indebted to Professor E. W. Walls for help in the preparation of this paper, to Dr. I. Mackenzie for making this foetus available for study, Mr. P. R. Runnicles for taking the photographs and to Dr. M. E. Carruthers for help with the dissection of the foetus.

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Addendum

Since this paper was prepared Bain and Scott (1960) have published a series of 50 cases with renal agenesis and other forms of severe urinary tract dysplasia. They report that seven of these had gross defects involving the caudal end of the foetus such as spina bifida or sirenomelia.

ALDRICH'S SYNDROME: FAMILIAL THROMBOCYTOPENIA, ECZEMA AND INFECTION

BY

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In 1954 Aldrich, Steinberg and Campbell described a family, originally of Dutch extraction, in which the male infants were liable to die at a young age having shown signs of 'draining ears, eczematoïd dermatitis and bloody diarrhoea' from the age of a few weeks. They briefly described the clinical features in one child who was a member of this family and who died. They went on to show quite clearly that if the condition which had killed previous male members of the family was the same (as the family itself maintained) then it must have been genetically determined. Since it affected only male members of the family and only some of them, they concluded that the condition must be due to a sex-linked recessive gene which was passed down through the females to the males (in the same way as haemophilia and pseudo-hypertrophic muscular dystrophy). They showed, too, that in the last three generations 16 out of 40 males had been affected and had died within the first 31 months of life. Further evidence of the genetic basis of the condition in Aldrich's family has been produced more recently by Krivit and Good (1959), who report that the two females who appear to carry the gene at the moment, and are reproducing, have produced eight children between them since Aldrich's paper was published. Two of them are girls and are normal, while six of them are boys, three of whom have been affected by the condition. This is what one would expect if it were due to a sex-linked recessive gene. It seems quite definite therefore that in the family described by Aldrich the condition is genetically determined in this way.

Meanwhile Huntley and Dees (1957) have described other white families in which the same condition appears to have been present, and Wolff and Bertucio (1957) have described it in a Negro family. Huntley and Dees contributed considerably

towards determining the clinical picture and they described the main features as being 'eczema associated with thrombocytopenic purpura and purulent otitis media'. They described five cases, all of whom died. In only two of these cases, however, was the genetic nature of the condition at all conclusive. These two cases (1 and 2 in their series) were brothers. In their Case 3 no family history was obtainable and in their Case 4 the child was adopted and no family history was available. In Case 5 there was a suggestive but unconvincing family history.

Although Wolff and Bertucio reported their Negro family in 1957, it was only briefly, and further details do not seem to have been published. It is possible therefore to include their family as one in which the abnormal gene is carried, but it is not possible to include the individual cases of the family in this review since full details are not available.

Very recently Mills and Winkelmann (1959) have reported a further three cases in two families. Again all the children were male and there was a strong family history in all of them. Two of them were cousins. All three have died.

To date, therefore, seven* families have been reported, who seem to carry this abnormal gene, and full details are available of 16† cases, some of whom do not have a positive family history but are clinically identical with those who do. All 16 were males and all are dead.

The object of the present communication is to report two cases in an English family which also seems to carry the abnormal gene. One has died and the other is still alive.

* Aldrich (1); Huntley and Dees (1); Krivit and Good (2); Wolff and Bertucio (1); Mills and Winkelmann (2).

† Aldrich (1); Huntley and Dees (5); Krivit and Good (7); Mills and Winkelmann (3).

Case Reports

Case 1. Patrick G. (54/23984/G) was born on September 30, 1949.

FIRST ADMISSION. On November 2, 1950, at the age of 14 months, he was admitted because of infantile eczema dating from the age of 4 months. This had affected mainly the head, arms, legs and neck. It had also been observed from the age of 4 months that he had a bleeding tendency and that unexplained bleeding had occurred from the nose, ears and gums. This was especially noted by the mother since she had had a brother who was said to have suffered from haemophilia and who died of pneumonia at the age of 1 year, in 1933.

The reason for Patrick's first admission was that some areas of the eczema had started to weep, the serous discharge being bloodstained, and that he had in addition many petechiae and ecchymoses.

The eczema responded well to the dermatologists' treatment but the purpura continued to appear and was shown to be related to a thrombocytopenia which (with the exception of one count) persisted until a splenectomy was performed three years later. The eczema, however, tended to improve and Fig. 1 shows only a quiescent eczema of the ankle, since it was taken primarily to show the purpura. He constantly had similar eczema behind the ears and inconstantly on the face.

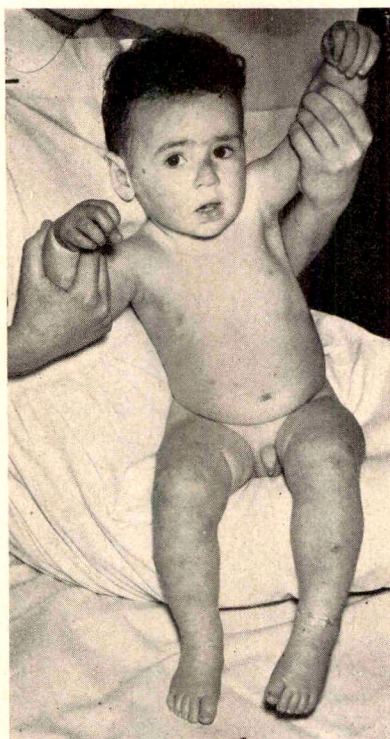


FIG. 1.—Case XVII. Patrick G. Shows severe ecchymoses and flexural eczema at ankles.

The only drug which the child had had before admission was phenobarbitone (for the irritation of his eczema), and withdrawal of this led to no improvement in the purpura.

During the first and subsequent admissions numerous references were made in the notes to the ease with which he picked up infections. He was febrile on many occasions, sometimes without any satisfactory explanation being found; on others he had recurrent otitis media, pyoderma, diarrhoea and respiratory infections.

On December 18, 1950 he was discharged home with a quiescent eczema but with an active purpura and thrombocytopenia. He was somewhat anaemic at this stage (Hb 9 g.%) and was given a course of oral iron. His white cell count was 11,000/c.mm. and remained normal throughout except for the polymorph response during the acute infections.

SECOND ADMISSION. He was re-admitted on April 21, aged 19 months, with a recrudescence of his eczema. His platelet count was 178,000/c.mm. (the only normal count obtained before splenectomy), but this rapidly fell again to a low level and the purpura (which had never really been absent) persisted. At this stage a marrow puncture was performed and was reported as showing 'plenty of platelet-forming megakaryocytes'.

On July 11, 1951 he was discharged for the second time, again with quiescent eczema but still thrombocytopenic.

THIRD ADMISSION. He was re-admitted on August 22, 1953, aged 3 years 11 months; the eczema was still quiescent but he had discharging ears, impetigo, bleeding gums and profuse purpura. His platelet count was still low. Once again the skin lesions cleared, and on this occasion he was given A.C.T.H. 25 mg. b.d. for 10 days (the 'ration' which was available at the time). Since the platelet count showed no response further supplies were not requested.

In view of the fact that this child was known to have had thrombocytopenia of severe degree for over three years without remission (other than for one count), it was felt that splenectomy was indicated and this was performed on December 7, 1953 (Mr. F. J. P. O'Gorman). There was an immediate rise in the platelet count, which at one time went to over 600,000/c.mm. and then stabilized at a normal level and remained normal till (at least) four days before he died. In association with this there was a complete disappearance of his purpura and bleeding tendency until the final illness. On January 14, 1954, he was discharged for the third time.

FOURTH ADMISSION. On January 26, 1954, 12 days after his third discharge, he was admitted as an emergency, having been gravely ill for 24 hours. He was unconscious with a low B.P. (55/0) and no fever. In spite of this the clinical condition seemed to be compatible with a septicaemia and he was treated accordingly. He proceeded to develop a pneumococcal meningitis and responded well to treatment. Once this was stopped he relapsed, and this time the meningitis was said to be

staphylococcal in origin. This also responded satisfactorily to treatment.

He was discharged home for the fourth time on April 4, 1954. His platelet count was still normal and it had been established that he did not have agammaglobulinaemia.

FIFTH ADMISSION. This was on July 5, 1954 for dental extractions which proceeded without incident.

When seen in the out-patient department on October 1, 1954, he was found to be well and without purpura. His platelet count was 228,000/c.mm.

SIXTH ADMISSION. He was admitted as an emergency on October 5, 1954, aged 5 years, having been ill for only 12 hours with symptoms similar to the illness of his fourth admission, but his condition had deteriorated very rapidly and on admission he was moribund. At autopsy he had bilateral adrenal haemorrhage of the kind found in the Waterhouse-Friderichsen syndrome. No proof of a septicaemia was obtained on this occasion.

SUMMARY. This boy showed signs of infantile eczema and purpura from the age of 4 months. A maternal uncle had suffered from a bleeding tendency and had died of pneumonia at the age of 1 year. The present patient's eczema persisted but tended to improve as the years went by; his purpura was associated with thrombocytopenia and they both persisted until splenectomy was performed at the age of 4 years 2 months. Thereafter the platelets rose to a normal level and the bleeding tendency disappeared. He had always tended to show signs of minor infections but some weeks after splenectomy he developed pneumococcal septicaemia with meningitis and then relapsed with a staphylococcal meningitis. He responded well to treatment. At the age of 5 years, 10 months after splenectomy, he still had a normal platelet count, but five days later he was admitted moribund having been ill for only 12 hours (again with symptoms suggestive of septicaemia) and he died shortly afterwards. Autopsy showed massive bilateral adrenal haemorrhage.

Case 2. Christopher G., brother of Patrick, was born on August 31, 1957.

Between the births of these two children (see the family tree in Fig. 2) a boy and a girl had been born, both of whom are perfectly healthy and show none of the manifestations of the condition.

Christopher was also thought to be normal until he was 3 months old when the family doctor (Dr. E. D. Forster) noted that he had petechiae on the neck (Fig. 3). At 4 months he was admitted for investigation and by that time he had some eczema behind the left ear although his eczema never became so severe as Patrick's. On admission he had a definite thrombocytopenia as a cause of his purpura and his ability to pick up infection was

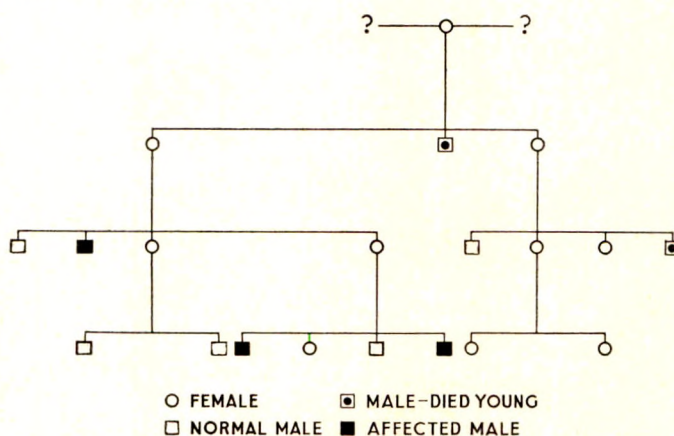


FIG. 2.—Shows G. family history as far as it can be constructed at the moment.

also demonstrated during his stay in hospital since he developed furunculosis, pyuria and frequent bronchitis but never otitis media. It was established that he also did not have agammaglobulinaemia and his white count throughout was normal.

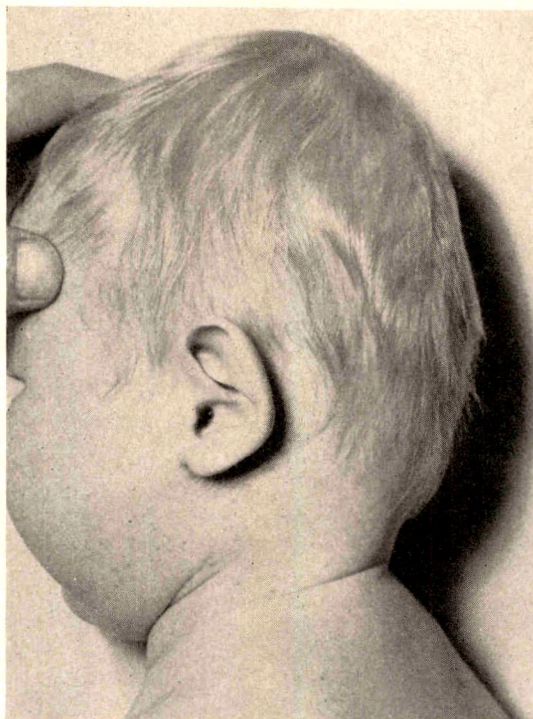


FIG. 3.—Case XVIII. Christopher G. Shows purpura on neck and minimal changes of eczema behind ear.

Marrow puncture was performed and reported as showing 'adequate megakaryocytes present but reduced platelet formation'.

Attempts to stimulate platelet formation by means of A.C.T.H. and prednisolone were only temporarily successful. In view of our experience with Patrick after splenectomy it was decided that this operation was not indicated in Christopher's case so he was discharged home, still with a low platelet count.

He has remained well since, apart from frequent respiratory infections during the winter months, and he is now a well developed toddler who still gets occasional crops of petechiae but whose eczema is well healed.

SUMMARY. Christopher G., brother of Patrick, had petechiae at 3 months and slight eczema at 4 months. He has always been liable to pick up infections. He has thrombocytopenia which only temporarily responds to

A.C.T.H. and steroids. He does not have agammaglobulinaemia. He is now (April, 1960) a healthy child with occasional petechiae and recurrent respiratory infections.

Charts showing the changes in the platelet counts in response to A.C.T.H., prednisolone and splenectomy in the two brothers are shown in Figs. 4 and 5.

Table 1 shows the main features in the 18 cases described so far. All the cases showed eczema but this was of variable severity.

All the cases showed purpura and, except for Case VIII, they all showed persistent thrombocytopenia, too. In Case VIII only one count was done and it was normal, but this may well have been a temporary spontaneous rise such as occurred in

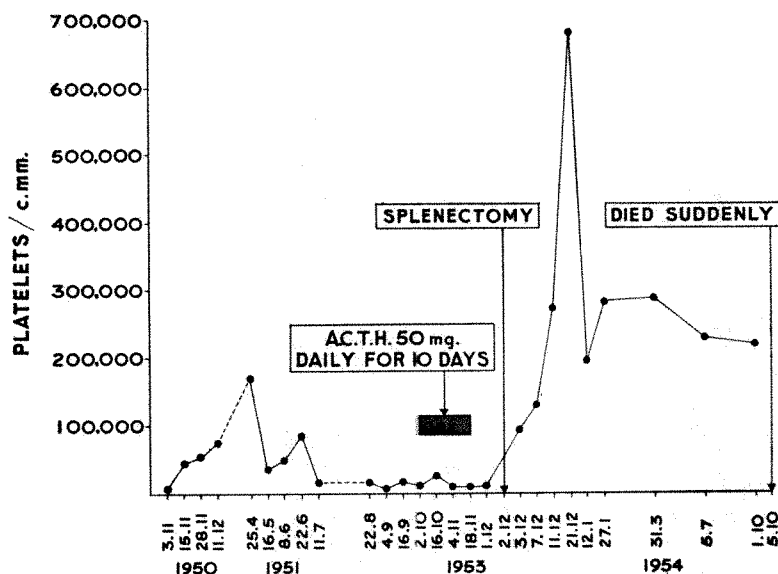


FIG. 4.—Shows platelet level over four years of Patrick G. with absence of response to A.C.T.H., and dramatic response to splenectomy which was maintained until at least four days before his sudden death.

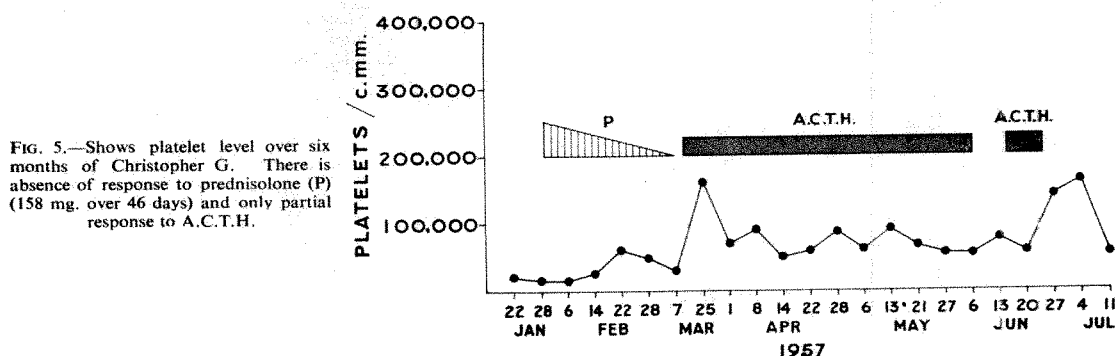


FIG. 5.—Shows platelet level over six months of Christopher G. There is absence of response to prednisolone (P) (158 mg. over 46 days) and only partial response to A.C.T.H.

TABLE I
ANALYSIS OF CASES REPORTED IN THE LITERATURE

	Case Number																	
	I	II	III	4	5	6	VII	VIII	9	X	11	12	XIII	XIV	XV	XVI	XVII	XVIII
Age at onset	1 m.	3 m.	5 d.	2 w.	2 w.	3 m.	5 m.	3 d.	1 d.	3 w.	11 d.	6 d.	9 d.	Birth	2 w.	2 w.	4 m.	3 m.
Age at death	11 m.	22 m.	2 yr.	14 m.	2 yr.	7 yr.	3 yr.	2 yr.	8 m.	1 yr.	20 m.	2 yr.	23 m.	15 m.	5 m.	3 yr.	5 yr.	A
Clinical features:																		
Purpura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thrombocytopenia ..	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+
Eczema	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Infections:																		
Pyoderma	+	+		+	+	+		+			+	+	+		+	+	+	
Pneumonia		+	+	+	+	+		+			+	+	+	+	+	+	+	
Otitis media	+	+	+	+	+	+	+		+	+	+	+	+		+	+	+	
Meningitis	+	+	+														+	
Septicaemia	+															+	+	
Pyrexia	+						+		+			+					+	+
Treatment of thrombo-																		
cytopenia:																		
A.C.T.H.			+		+					+							+	+
Steroids			+			+				+		+				+		+
Splenectomy	+	+	+		+	+				+				+	+	+	+	+
Mode of death	H	I	I	I	H	I	H	H	I	H	I	I	I	I	I	I	H	A

Cases with strong family histories in Roman numerals, those without in Arabic. Case I is Aldrich's original case; Case XIII Krivit and Good's follow-up of Aldrich's family; Cases II-6 are those of Huntley and Dees; Cases VII-XIII are those of Krivit and Good; Cases XIV-XVI are those of Mills and Winklemann; Cases XVII and XVIII are described in the present communication. We have not been able to trace details of Wolf and Bertuccio's family.
H = death from haemorrhage; I = death from infection; A = alive.

Patrick. The thrombocytopenia is very important diagnostically since it is the only positive laboratory finding which occurs as an essential part of the syndrome.

Infection of one kind or another occurred in all the cases and was responsible for at least 11 of the deaths which have occurred. It should be noted how frequently otitis media has been present but this is almost certainly a reflection of these children's poor resistance to infection rather than of any specific defect in their middle ears.

Since the family history is so important cases with a strongly suggestive family history have been numbered in Table I differently from those without. The two cases recorded in the present communication, apart from being brothers, had an uncle who died in infancy apparently from the same condition. The mother of that child, i.e. the grandmother of our two cases, is alive and has given a detailed account of him. He died of pneumonia at the age of 1 year (1933) but before then she was told by the family doctor that he suffered from 'haemophilia'. This was because he bled very easily and he frequently came out in 'large bruises just like Patrick's'. The rest of the family history (Fig. 2) shows that two other male children died young but there was no evidence to show that they had either a haemorrhagic tendency or eczema.

Unfortunately no further family history is available since the grandmother, Mrs. T., went to New Zealand as a child (her parents having died) and

she has completely lost touch with her mother's family. She thinks that her mother had some sisters but does not know where their descendants might be.

Discussion

Although the various clinical aspects of this condition occur separately, and some of them quite commonly, it is unusual for them all to occur in one individual and certainly in members of the same family. Long before we read the original papers on this subject we had decided that this was an unusual family. There are four main features of the condition and they will be discussed separately. In each case the patient has been a male and the symptoms have appeared within the first six months of life.

Thrombocytopenia. This has led to the most common symptom, namely, bleeding. This includes purpura, epistaxis, 'bloody diarrhoea', haematuria, bleeding gums and cerebral haemorrhage, in fact any of the manifestations of bleeding which occur with thrombocytopenia at any age. Six of the 17 deaths appear to have been due to haemorrhage but in two of these (including Patrick) the haemorrhage was into the adrenals and may have been secondary to a fulminating septicaemia.

The cause of the thrombocytopenia in these cases is no clearer than it usually is in 'essential thrombocytopenia'. There are certainly adequate numbers

of megakaryocytes present in the bone marrow so that either they do not produce enough platelets or the platelets they do produce have a shorter life than normal. The latter could result either from a defect in the platelets themselves or from the presence of a platelet-agglutinating antibody. No evidence of such an antibody was found in two of Krivit and Good's patients and, in any case, if the condition is genetically determined some congenital defect in the production or formation of platelets seems more likely than excessive destruction of normal platelets.

We do not even know yet whether the condition is congenital or not. Since the only part of the syndrome which is likely to be present at birth is the thrombocytopenia, it will be necessary to do platelet counts on the cord blood of future infants born to the affected families. Although Case XIV is shown as having symptoms from birth, this information was based on the mother's history and not on observation.

Eczema. This appears to be identical with the usual infantile eczema except that in certain cases bleeding has occurred into the eczematous areas. The severity of the skin lesions has varied from time to time even in one patient and has varied considerably from one patient to another. Even in our two brothers the eczema was more severe in Patrick than in Christopher. Mills and Winkelmann (1959) point out that the eczema is the least specific of the clinical features in these children and we agree with this.

Liability to Infection. This is the most difficult part of the syndrome to define, since, of course, most infants in the first year of life are liable to pick up infections. The infections which these affected babies have are of the usual variety and include pyoderma and respiratory infections in addition to the otitis media which has occurred in nearly every case. It is characteristic of these children, too, that they run fevers for which no satisfactory explanation can be found. It can be seen from Table 1 that a considerable number die from infections in spite of antibiotic therapy. This has occurred in those on whom splenectomy has not been performed (Cases 4, 9, 11, 12, XIII, XIV, XVI) as well as in those whose spleens have been removed (Cases II, III, 6, XV, XVII). It is well known that King and Shumacker (1952) and Smith, Schulman, Stern and Erlandson (1956) have suggested that splenectomy in young children may be followed by death from fulminating infection. In Smith's series this occurred in 28% of his 50 patients who had had splenec-

tomy performed under the age of 2 years for any reason at all, including trauma. In spite of the fact that there is evidence against this contention (Gofstein and Gellis, 1956) as well as in favour of it, we felt that splenectomy should not be undertaken in Christopher. Krivit and Good (1959) are also of the opinion that there is an increased liability to severe infection after splenectomy. They were, however, unable to find any alteration in known immune mechanisms in two of their cases on whom intensive investigations were performed. In all cases on whom gamma globulin estimations have been performed it has been found to be present in normal amounts, and the white cell counts have also been normal. There is therefore no explanation for the liability of these infants to infection.

Family History. There have now been reported eight families showing both the clinical features of Aldrich's syndrome and the family history, which is strongly suggestive of its genetic basis. In the other cases all the affected children have been males but there has been no clear-cut history of the condition occurring in other male relatives. Since it was the genetic basis of the condition which Aldrich laid down, it seems wise to limit the syndrome bearing his name to those cases in which there seems to be a reasonable certainty that, in addition to occurring in males, it has been genetically determined by a sex-linked recessive gene.

It is, of course, often found that conditions such as infantile eczema are familial, and they are often thought to indicate a familial tendency to allergy. Thrombocytopenia, too, is often thought to have an 'allergic' basis and it is not surprising that American writers have concentrated on the possibility of one allergic factor being responsible for both parts of the syndrome. Although in certain cases true allergic responses have been obtained, there does not appear to be any clear-cut evidence that the symptoms are due to any specific antigen-antibody reaction. Following the usual British practice at the present time, skin reactions, etc. were not performed on either of our two patients so that information on this point is not available.

As with all familial conditions, the parents and relatives all worry about what is likely to happen to future children who are born into the family. Once the genetic basis becomes clear, as we believe it has in this syndrome, it becomes easier for the physician to give the family the facts, as far as they are known, and this can reassure the relatives considerably even though they realize that half of the further male children may be affected.

It is customary, whenever someone is writing

about a relatively new syndrome, to say that cases are likely to be found more frequently in the future once people start looking for them. This is not likely to happen to any great extent in Aldrich's syndrome since, although other families will probably be described, it is unlikely that they are at all numerous. The importance of the syndrome lies more in the fact that it is a newly recognized disease process due to a sex-linked gene, and the components of the syndrome all occur fairly commonly as separate entities.

Summary

A further family is reported which seems to suffer from Aldrich's syndrome.

The syndrome consists of thrombocytopenic purpura, eczema and infection occurring in male infants and leading eventually to death from haemorrhage or infection. It is genetically determined and is due to a sex-linked recessive gene.

It has not yet been shown whether or not the condition is congenital.

I would like to thank Dr. H. R. Vickers and Dr. I. B. Sneddon for their cooperation in the management of the children, Dr. A. J. N. Warrack for the autopsy findings, Dr. S. Varadi for the reports on the bone marrow and for helpful advice, and Dr. E. D. Forster for his great assistance with the family.

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EFFECT OF CORTICOTROPHIN ON HYPOTHALAMIC SYNDROME IN CHILDREN

BY

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Bauer (1954), in reviewing 60 cases of hypothalamic syndrome reported at all ages in the literature, named the principal signs in descending order of frequency as precocious puberty, hypogonadism, diabetes insipidus, psychic disturbances, somnolence, obesity, thermodysrregulation, emaciation, convulsions, sphincter loss, bulimia, anorexia and dyshydrosis. Some of the above signs are clearly due to abnormal secretion by the pituitary gland, and those specifically resulting from a deficiency of adrenocorticotrophic hormone might be expected to respond to replacement therapy since the value of corticotrophin (or of cortisone) is well established in the prevention and treatment of hypopituitary coma (Caughey, 1958). The pituitary gland is under the control of the hypothalamus and it is not clear whether certain signs are due purely to hormone deficiency or to direct interference with the hypothalamic vegetative centres; this applies to disturbance of appetite and body weight, mental alertness and body temperature. Damage to hypothalamic centres by an astrocytoma causes emaciation and increased appetite in the syndrome described by Russell (Russell, 1957; Kagan, 1958); these symptoms do not respond to corticotrophin in spite of other evidence of depression of pituitary function. Damage to the vegetative centres probably also explains the failure to respond to corticotrophin or cortisone in some cases of collapse following operation in the hypothalamic region (Northfield, 1955).

We now report four cases of hypothalamic syndrome in whom a stuporose state responded well to treatment with corticotrophin, which suggests that the underlying cause might be anterior pituitary deficiency rather than damage to the vegetative centres. Anorexia and wasting, which accompanied the stuporose state in two of the cases, also responded to corticotrophin. A space-occupying lesion at the base of the brain was accompanied

in all these cases by an endocrine disturbance, in three cases by diabetes insipidus and in one by precocious puberty.

The four cases came under the care of Mr. Wylie McKissock at The Hospital for Sick Children, Great Ormond Street.

Case Reports

Case 1 (R.S.). At the age of 9½ years this boy had a convulsion with residual weakness of the left arm. Two and a half years later he developed diabetes insipidus. He was admitted to The Hospital for Sick Children, Great Ormond Street. After air studies had been carried out it was concluded that there were intracranial lesions in the right frontal and pineal regions. A large port-wine naevus over the right forehead indicated that cerebral angiomas were probably present. During the next year the patient became progressively listless. Papilloedema developed and a further ventriculogram carried out in Sweden confirmed multiple intracranial lesions (Professor Olivecrona). The basal metabolic rate was found to be minus 34 per cent. Thyroid extract effected an improvement. Eight months later he was readmitted to The Hospital for Sick Children, Great Ormond Street, having been doubly incontinent for a month. His fluid intake, previously high, was estimated to have gone down to approximately one litre daily and he was refusing food. He was found to be in a grossly wasted, stuporose and apathetic state. He was hypothermic (oral temperature 95° F. (35° C.)) and the blood pressure was 60/40 mm. Hg. The urinary 17-ketosteroid excretion was 1·2 mg./24 hours and the 17-hydroxysteroids were 2·7 mg./24 hours.* The blood cholesterol was 98 mg. per 100 ml. A glucose tolerance test gave the following figures: fasting 82 mg., and then at 30-minute intervals after an initial 50 g. of oral glucose, 91, 132, 176, 252 and 169 mg. per 100 ml. Plasma

* In our laboratory the normal range for 17-ketosteroids for children of 9 to 12 years is 1·1–9·5 mg./24 hours, mean 3·8 mg./24 hours; and for 17-hydroxysteroids, 1·0–8·2 mg./24 hours; mean 3·8 mg./24 hours.

electrolyte values were all increased; the plasma sodium was 136 mEq./l., the plasma potassium 5.9 mEq./l. and the plasma urea 137 mg. per 100 ml.

PROGRESS AFTER CORTICOTROPHIN. Replacement therapy was started with corticotrophin 20 mg. b.d. The fluid intake was raised to 3½ l. daily to counteract hyperelectrolytaemia, but pitressin was not given at this stage. The calorie intake was kept at approximately 2,000 calories, using a fortified dried milk preparation with added vitamins (Complan). During the next two days the patient became more alert, his oral temperature rose to normal and the blood pressure increased to 130/70 mm. Hg. There was a good eosinophil response to the first dose of corticotrophin with a fall from 238 to 128 per c.mm. in four hours and subsequently to 40 per c.mm. The urinary 17-ketosteroids rose steadily to 9.3 mg./24 hours, and the 17-hydroxysteroids to 25.4 mg./24 hours. Corticotrophin was then cut down by stages to 5 mg. daily and on this dosage the patient's condition remained greatly improved. The output of urine was now 2.3 l. daily. The hyperelectrolytaemia remained unchanged. The fluid intake was therefore increased to 5 l. daily and pitressin was started in a dosage of 1 unit daily. Four days later the patient rapidly became disorientated and then comatose. It was thought that this was probably due to overhydration. Intravenous saline was given, followed, as he improved, by sodium chloride orally and D.O.C.A. 5 mg. daily by injection. Subsequently he began to lose salt through the kidney, and sodium chloride by mouth and D.O.C.A. were relatively ineffective in maintaining the plasma sodium chloride level in equilibrium. It was thought that a cerebral salt-wasting syndrome had developed, though the possibility of salt loss induced by overhydration could not be excluded. Two months later a ventriculogram was done with a view to a subsequent brain biopsy. Two hours after ventriculography the patient became profoundly unconscious and there was an abrupt fall in the excretion of sodium. This collapse was presumably due to damage to the vegetative centres. He died in coma two weeks later.

At autopsy (Dr. Martin Bodian) the diagnosis of cerebral angioma was confirmed. The hypothalamus was involved by an angioma but this was not invading the pituitary gland.

COMMENT. In this boy with a cerebral angioma involving the hypothalamus, improvement in alertness, weight and appetite showed that corticotrophin had been of benefit. Long-standing diabetes insipidus later became complicated by a salt-losing syndrome and further damage to the vegetative centres led to coma and death.

Case 2 (M.H.). This girl, aged 10½ years, had a year's history of lethargy, poor appetite and loss of weight, with headaches and vomiting for six months. The child was admitted to The Hospital for Sick Children, Great Ormond Street, where ventriculography showed a suprasellar space-occupying lesion largely blocking the third

ventricle. She was transferred to the National Hospital for Nervous Diseases, Queen's Square, where an inoperable suprasellar tumour was found and was implanted with radioactive gold seeds. Post-operatively she developed a right hemiparesis. She became very drowsy and the blood pressure fell to 70/50 mm. Hg. Next day her condition was still stuporose and the oral temperature was 94° F. (34.4° C.). At this time the plasma sodium was 131 mEq./l., potassium 5.1 mEq./l. and urea 75 mg./100 ml. Urinary steroid levels were low; 17-ketosteroid excretion was 0.7 mg./24 hours and 17-hydroxysteroids were less than 1.0 mg./24 hours. The plasma cholesterol was 276 mg. per 100 ml.

PROGRESS AFTER CORTICOTROPHIN. Therapy was commenced with 10 mg. b.d. of corticotrophin, subsequent to which the temperature rose progressively to 98° F. (36.7° C.) and she became much brighter. Right hemiparesis and dysphagia remained. A month after the operation marked thirst was first noticed and found to be due to diabetes insipidus. Pitressin was not given at this stage. Two weeks later corticotrophin was reduced to 10 mg. daily and she was sent away for one month's convalescence. On her return she was found to be obese (weight gain 5.9 kg.) and was noticed to show excessive hunger and unpredictable changes of mood. The plasma electrolyte levels were within normal limits. The urinary 17-ketosteroid excretion was 10.8 mg./24 hours. Corticotrophin was discontinued, but during the subsequent week the patient again developed anorexia, apathy and a tendency to sleep during the day. Corticotrophin was recommenced in a dosage of 10 mg. every other day with good effect. She went out of hospital well stabilized on this dose and also on pitressin snuff 30 units daily. After a further three months corticotrophin was gradually reduced and she was doing well on pitressin alone six months later.

COMMENT. In this case of hypothalamic syndrome due to suprasellar tumour, lethargy and hypothermia responded well to corticotrophin. The patient's requirements fell rapidly but attempts to withdraw the drug after three weeks were unsuccessful, though treatment was successfully discontinued three months later. Diabetes insipidus developed post-operatively. This was the only case in the series in which urinary steroid excretion was below normal before treatment.

Case 3 (P.H.). This girl, aged 10 years, had a history of excessive thirst and polyuria for three years. Deterioration of vision had been present for two years, culminating in complete blindness in the right eye one month before admission. Headaches, vomiting and somnolence were recent features. On admission to The Hospital for Sick Children she was drowsy but cooperative. The blood pressure was 95/60 mm. Hg. The urinary specific gravity never rose above 1.003 and a diagnosis of diabetes insipidus was made. Ventriculography showed a space-occupying lesion in the pituitary-hypothalamic region. Craniotomy revealed a dark red

mass which appeared to be welling from the pituitary fossa. Removal was impossible. It had the appearance of a teratoma and this was confirmed histologically. After the operation she remained drowsy, waking only to be fed. Body temperature was normal. The plasma sodium was 134 mEq./l. and plasma potassium 4.4 mEq./l. The urinary 17-ketosteroids were 3.5 mg./24 hours and the 17-hydroxysteroids 2.2 mg./24 hours.

PROGRESS AFTER CORTICOTROPHIN. Corticotrophin, 20 mg. b.d., was given in view of the drowsiness. Within 48 hours she became much more alert with an increased appetite and by the fourth day she wanted to get out of bed. The urinary 17-ketosteroids rose to 17.9 mg./24 hours and the 17-hydroxysteroids to 41.7 mg./24 hours. Corticotrophin was gradually withdrawn after 10 days, and five days after the last dose she was transferred to another hospital for radiotherapy. The drowsiness returned rapidly but again responded promptly to corticotrophin, which was discontinued after three weeks, this time without any recurrence of symptoms. Nine months later she remained well.

Before craniotomy the average daily urinary output in this patient was 1.4 l., rising to 2.2 l. during the five days following operation; after five days on corticotrophin it reached 9.7 l./24 hours, whereupon corticotrophin was withdrawn. No pitressin was being given at this time.

COMMENT. As in the previous case corticotrophin was principally of benefit post-operatively in improving the alertness of a patient with suprasellar tumour and diabetes insipidus. A relapse occurred during radiotherapy but a second course was needed for only three weeks and the patient was well apart from diabetes insipidus nine months later.

Case 4 (D.R.). The patient was a boy aged 9 years. At the age of 8 years pubic hair and enlargement of the penis were noticed. Six months later vomiting began. Five weeks before admission he had two major convulsions and thereafter developed headaches, anorexia, lassitude and a squint. On admission he answered questions readily, though he was otherwise lethargic and content to lie in bed all day. He was emaciated (weight 48 lb. (21.8 kg.)) (Fig. 1). The penis and testes were of adult proportions. The temperature was normal and the blood pressure 140/90 mm. Hg. The plasma sodium was 132 mEq./l. and the plasma potassium 5.1 mEq./l. The urinary 17-ketosteroids were 2.6 mg./24 hours and the 17-hydroxysteroids 5.9 mg./24 hours. A glucose tolerance test was normal with a fasting level of 97 mg. and at 30-min. intervals after 25 g. of glucose 97, 156, 135, 97, 103 and 97 mg. per 100 ml. Ventriculography showed space-occupying lesions in the left subfrontal and suprasellar regions; there was also internal hydrocephalus and the presence of a third lesion in the posterior fossa was suspected. Craniotomy was not undertaken because of multiple lesions. During the next two weeks the patient remained lethargic and his emaciation continued in spite of adequate fluid and calorie intake with 'complan' via a nasal catheter.

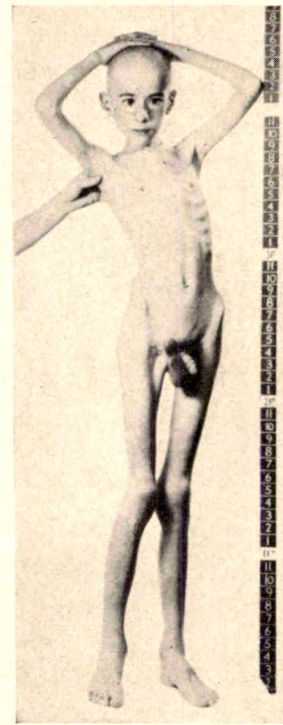


FIG. 1.—Case 4. On admission. Note gross emaciation and sexual precocity.

PROGRESS AFTER CORTICOTROPHIN. Corticotrophin 20 mg. daily was then given. Six days later he was less lethargic, gaining weight and feeding himself. The



FIG. 2.—Case 4. Shows response of emaciation to corticotrophin.

urinary 17-ketosteroids were 6.1 mg./24 hours and the 17-hydroxysteroids 6.2 mg./24 hours. His weight increased slowly to 61 lb. (27.7 kg.) a month later. He was by then fully alert but not euphoric. He was transferred to another hospital for deep x-ray therapy after which corticotrophin was gradually withdrawn. Three months later his clinical condition remained good and he has continued to improve (Fig. 2).

COMMENT. Here, as in Case 1, lethargy and emaciation were associated with a suprasellar lesion as part of multiple inoperable intracranial lesions. A rapid response occurred to corticotrophin, which was later withdrawn successfully after radiotherapy. Isosexual precocity was also a feature.

Discussion

The fact that the administration of corticotrophin coincided with correction of stupor and improvement in the general condition of all four patients suggests that there was an initial depression of pituitary adrenocorticotrophin secretion for which corticotrophin acted as a replacement. However, laboratory investigations provided little confirmatory evidence of adrenocortical deficiency. Glucose tolerance tests in two of the patients did not show the typical change of hypoglycaemia over-responsiveness. Insulin tolerance tests were not performed. The eosinophil response after corticotrophin was measured in Case 1; this was normal, whereas in hypopituitarism a delayed or diminished depression of the eosinophils from secondary adrenocortical failure may occur, depending upon the duration of the pituitary failure (Nabarro, 1957). In our cases the plasma sodium and potassium levels did not show changes typical of adrenocortical failure. There was no delayed increase in steroid excretion after corticotrophin was administered. Two cases (1 and 3) showed a marked diuresis after the administration of corticotrophin, but this is not strictly evidence of initial depression of adrenocorticotrophic hormone secretion since a rise in solute excretion may occur consequent upon an increase in appetite. On a fixed dietary intake corticotrophin will not influence urinary volume in cases of anterior and posterior pituitary deficiency (Leaf, Manby, Rasmussen and Marasco, 1952). The overhydration which occurred in Case 1 was due to excess intake of water and pitressin and not to lack of corticosteroids since at that time corticotrophin had already been administered and steroid excretion was well within the normal range. The special investigations therefore showed no major deficiency in those aspects of the pituitary-adrenocortical mechanism which could be investigated.

Cases of post-operative coma due to tumours in and around the pituitary gland have previously been reported to respond to steroid replacement; in contrast to our cases, these usually showed evidence of long-standing pituitary deficiency and required permanent substitution therapy. In our three cases, who survived, corticotrophin was withdrawn successfully. If, as seems likely, there was no permanent or severe damage to the hypothalamic anterior pituitary system in our cases, the response to corticotrophin must be explained on a different basis. Two possibilities might account for the beneficial effect. First, the improvement may have been due to excessive secretion of corticosteroids which the corticotrophin stimulated. Corticosteroids improve the appetite and alertness in normal subjects. An alternative explanation is that there was a temporary depression of adrenocorticotrophic hormone, not shown in our tests, and that this was reversed by the general improvement which followed hormonal and surgical treatment. Full assessment of anterior pituitary activity was handicapped in two ways; first, by the ill state of the children which precluded full endocrine investigations, and second, by the fact that they had not reached the age of puberty; after puberty the recognition of hypopituitarism may be made more easy by such signs as hypogonadism, loss of pubic and axillary hair and low steroid excretion.

Whatever the explanation, the amelioration in the stupor and general condition of the four children was striking and it appears advisable to administer corticotrophin to children with lesions in the hypothalamic-pituitary region before surgery is undertaken. All our cases had an associated endocrine abnormality, such as diabetes insipidus or precocious puberty, though in one child the endocrine defect did not appear until post-operatively; this is in contrast to one case of suprasellar tumour we have seen recently in a boy of 9, who showed no associated endocrine defect and in whom the wasting and stupor did not respond to corticotrophin.

Summary

The response to treatment with corticotrophin is described in four cases of hypothalamic syndrome, i.e. children with space-occupying lesions at the base of the brain associated with endocrine disturbances, stupor and wasting.

The difficulties of diagnosing anterior pituitary deficiency in the pre-pubertal child are discussed and it is suggested that all children with lesions in the region of the hypothalamus and pituitary gland should be given corticotrophin (or cortisone) before surgical intervention.

We should like to thank Mr. Wylie McKissock for permission to study these cases, Professor A. A. Moncieff and Dr. W. W. Payne for their advice, and the Research Committee of the hospital for its support.

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SERUM PROTEIN PATTERN IN INFANTS WITH NUTRITIONAL DISORDERS

BY

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Paper electrophoresis for studying the serum protein pattern is of particular value in infancy because of the small volume of blood required. Despite improved methods of diagnosis and increased knowledge of the aetiology of wasting disorders in infancy, some cases of failure to thrive still present diagnostic difficulties. Cases in which diarrhoea, respiratory infection and wasting are associated are common, and in many such cases investigation of pancreatic function shows this to be depressed. After suitable treatment, which may include pancreatin, these infants are found on reinvestigation to have normal pancreatic function. Fibrocystic disease of the pancreas can then be excluded.

The present investigation was undertaken to find out if the serum protein pattern would be of any diagnostic value in wasted infants in whom the exact diagnosis was in doubt.

Methods and Material

Electrophoretic separation was carried out in a vertical tank of the type described by Flynn and De Mayo (1951), using a barbiturate buffer of pH 8.6. The samples of 0.05 ml. serum were run for 16 hours at a current of 0.25 mA per centimetre width of paper. Whatman paper No. 31M extra thick was used throughout. After drying, the strips were stained for 16 hours in 0.01% bromophenol blue according to the method of Block, Durrum and Zweig (1955). The individual fractions were estimated by the method of Levin and Oberholzer (1953), which involves the estimation of the nitrogen in each fraction after the strips have been divided. A correction for the nitrogen in the paper was made by estimating the nitrogen in a measured length of paper from protein-free areas at the ends of the strips. The sum of the individual fractions was checked with the total serum protein as determined by the micro Kjeldahl method.

The sera of 67 infants were examined. Twenty were normal infants known to be taking a satisfactory diet; they were free from infection and of normal weight. These infants served as controls and ranged in age from

7 weeks to 10 months. The other 47 infants were divided into four groups according to the main presenting symptom. Sixteen were wasted infants whose failure to thrive was attributed to underfeeding. Infection was not a complicating factor in these cases which were usually the result of maternal ignorance, though in a few cases actual neglect was involved. The second group consisted of nine infants with acute diarrhoea. The sera of these cases was examined as soon as their clinical condition permitted, in all cases after adequate re-hydration. Only severe cases with marked loss of weight were included. Thirteen were cases of chronic or recurrent diarrhoea. Most of these had a history of repeated bouts of diarrhoea over the previous few months. No single attack was usually of sufficient severity to warrant hospitalization, but advice was eventually sought on account of the frequent recurrence of symptoms and the failure to gain weight, or actual loss of weight, over a long period of time. The remaining nine infants suffered from chronic or repeated respiratory infections of varying severity. The attacks were usually accompanied by pyrexia and were often of sufficient severity to require treatment with antibiotics. In general this group of infants had maintained their weight somewhat better than the other groups and their average age was greater.

An attempt to assess the pancreatic function in these infants was also made by means of amino-acid absorption curves after a gelatin meal and when possible by duodenal intubation and measurement of the tryptic activity of the duodenal contents (Bate and James, 1956; unpublished data). The amino-acid curves were performed according to the method of West, Wilson and Eyles (1946). The criterion of normality was a rise in blood amino nitrogen to a level of at least 3 mg. per 100 ml. above fasting values at some time during the first one and a quarter hours after the gelatin was given. This increase in amino nitrogen was sustained for two and a half hours after the feed in normal infants, after which the level fell towards the fasting values.

Results

The serum protein patterns in normal infants and in those with chronic nutritional disturbances are

TABLE 1
SERUM PROTEIN LEVELS IN NORMAL INFANTS AND IN INFANTS WITH NUTRITIONAL DISTURBANCES

	Total (g. %)	Albumin (g. %)	Globulins				Average Age	Cases
			α_1 (g. %)	α_2 (g. %)	β (g. %)	γ (g. %)		
Normals	6.392	3.825	0.327	0.837	0.775	0.617	7 mth.	20
S.D.	0.66	0.41	0.06	0.10	0.11	0.15		
Undernutrition	6.171	3.125*	0.477†	0.902	0.865	0.802§	7 mth.	16
S.D.	0.71	0.45	0.28	0.30	0.19	0.42		
Acute diarrhoea	5.669	3.016*	0.378	0.872	0.767	0.634	7 mth.	9
S.D.	0.69	0.49	0.13	0.15	0.25	0.12		
Chronic diarrhoea	5.980	2.955*	0.504*	0.980§	0.807	0.732	6 mth.	13
S.D.	0.63	0.53	0.17	0.25	0.18	0.27		
Respiratory infections	6.308	3.357‡	0.394	0.970	0.778	0.806	13 mth.	9
S.D.	0.73	0.46	0.13	0.18	0.41	0.41		

* $P=0.001$; † $P=0.01$; ‡ $P=0.02$; § $P=0.05$

shown in Tables 1 and 2. Analysis of the results showed no significant variation from the normal in the total protein or beta globulin and only slight variations in the alpha 2 and gamma globulin. In all groups the albumin levels were significantly lower than in the controls. The alpha 1 globulin was significantly raised in the cases with chronic diarrhoea and undernutrition. The pattern was similar in all the abnormal groups; a depression in albumin levels was the most striking feature with a less pronounced increase in alpha 1 globulin. The rather higher albumin levels in the infants with chronic respiratory infection was probably due to the older age in this group.

The group with chronic diarrhoea also showed the most marked loss of weight as measured by the percentage of expected weight at the time of their first attendance.

The distribution of the amino-acid curves and the titre of duodenal trypsin in the various groups were also established, and are shown in Table 3. Only two infants with chronic diarrhoea had normal

curves and all had trypsin titres of under 1:200. The findings in cases with acute diarrhoea markedly resembled those in chronic respiratory infection and these cases did not show the marked impairment of pancreatic function of the infants with chronic diarrhoea. Unfortunately not all the cases of undernutrition were intubated and only 13 had amino-acid

TABLE 3
DISTRIBUTION OF TRYPSIN TITRE AND RESULTS OF AMINO-ACID ABSORPTION CURVES

No. of Cases	Amino-acid Curve		Trypsin Titre		
			Under 1:200	1:200	Over 1:200
	Normal	Abnormal			
16 Undernutrition* ..	4	9	2	1	5
9 Acute diarrhoea ..	4	5	—	2	7
13 Chronic diarrhoea ..	2	11	13	—	—
9 Respiratory infection ..	4	5	—	3	6

* In this group eight infants were intubated and 13 had amino-acid curves.

TABLE 2
SERUM PROTEIN PATTERN IN NORMAL INFANTS AND IN INFANTS WITH NUTRITIONAL DISTURBANCES (PERCENTAGE VALUES)

	Albumin	Globulins					% of Expected Weight
		α_1	α_2	Total α	β	γ	
Normals	59.8	5.1	13.2	18.3	12.1	9.6	
S.D.	1.4	1.3	1.4	2.1	1.7	2.3	
Undernutrition	50.8	7.7	14.4	22.1	14.0	13.0	73.3
S.D.	6.5	3.1	4.2	5.7	2.9	6.7	
Acute diarrhoea	53.1	6.6	15.4	22.0	13.4	11.2	79.3
S.D.	6.7	2.2	2.8	4.0	3.6	1.7	
Chronic diarrhoea	49.2	8.6	16.3	24.9	13.7	12.0	69.9
S.D.	5.5	3.4	3.9	5.8	4.0	4.3	
Respiratory infections	52.7	6.2	15.4	21.6	12.5	12.7	82.2
S.D.	4.8	1.9	4.6	4.4	2.8	5.6	

curves. From the available results it appears that with regard to pancreatic function this group lay between those infants with chronic diarrhoea and the other two groups. In only one case of chronic diarrhoea was tryptic activity present in a titre of over 1:50 and in four infants no activity could be detected.

The relationship of the percentage of serum albumin to the percentage of expected weight and to the titre of duodenal trypsin is shown in Table 4.

TABLE 4
RELATIONSHIP OF PERCENTAGE SERUM ALBUMIN TO PERCENTAGE OF EXPECTED WEIGHT AND TITRE OF DUODENAL TRYPSIN

	% Albumin	No. of Cases
% Expected weight		
Below 70%	48.8	12
70-80%	52.7	25
Over 80%	50.1	10
Titre of trypsin		
Below 1:200	48.5	15
1:200	50.3	6
Over 1:200	53.5	18

The figures for the relation between the titre of duodenal trypsin and the percentage of serum albumin are somewhat misleading. From them it might be assumed that the two bore a direct relation to each other. Whilst in general infants with very low or absent trypsin had low albumin levels there were exceptions to this and some infants with satisfactory trypsin titres had albumin levels of under 50%. The level of serum albumin does not therefore appear to be directly related either to the weight loss or to the degree of pancreatic dysfunction.

Discussion

Consideration of the results makes it clear that whatever the primary cause of the failure to thrive, the changes in the protein pattern are similar, the differences being of degree rather than of quality. The albumin showed a marked fall in all groups, alpha globulin showed a slight increase over normal values and gamma globulin tended to increase. These findings are in agreement with those of other authors who have determined the serum protein pattern in chronic nutritional disturbances. Gollan (1943) reported low albumin and raised globulins in chronic malnutrition in infants but he did not fractionate the globulins. Burgio and Giacalone (1953), investigating infants with nutritional atrophy, reported low albumin values with a striking increase in alpha globulin. Yoshida (1953) found low albumin levels and raised alpha and gamma globulin fractions. Jaso, Iturriaga and Roldan (1954)

studied two groups of infants, cases of toxicoses (i.e. acute gastro-enteritis) and cases of nutritional dystrophy. In both groups the albumin was low and alpha and gamma globulins raised compared with the normal. Carletti (1955) found low albumin and increased alpha globulins in both acute and chronic nutritional disturbances. The gamma globulin was either normal or elevated. Hallman, Kauhito, Louhivuori and Uroma (1952), Homolka and Mydlil (1955), and Schiavini and Sacconaghi (1956) investigated cases of acute gastro-enteritis, and these workers all found lowered albumin, raised alpha globulin and occasionally raised gamma globulin. Lubchez (1948) described the serum protein changes in a variety of infections in childhood. These were similar to those reported above. The changes in the serum protein pattern seem to be essentially similar in infants with nutritional disturbances whatever the primary cause. Grossman, Sappington, Burrows, Laviets and Peters (1945) and Peters (1946) have stated that pyrexia *per se* does not cause nitrogen loss. Nevertheless, large amounts of nitrogen are lost during acute illnesses, and this loss is continued after the temperature has returned to normal. This factor cannot be ignored when considering the hypoalbuminaemia of acute infection. Madden, Winslow, Howland and Whipple (1937) found that sterile turpentine abscesses markedly inhibited the regeneration of plasma proteins in animals depleted by plasmaphoresis even when given an adequate diet. They suggested a disturbance of the synthesizing mechanism as a cause for this failure.

There is considerable controversy over the state of pancreatic function in nutritional disorders in infancy. All authorities agree that enzyme secretion is depressed in severe protein malnutrition (Veghelyi, 1948; Thompson and Trowell, 1952; Dean and Schwartz, 1954; Gomez, Galvan, Cravioto and Frenk, 1954; Mukherjee and Werner, 1954; Scrimshaw, Behar, Perez and Viteri, 1955). From reports dealing with infants with other conditions it appears that pancreatic enzymatic activity is often depressed in acute and chronic diarrhoea and sometimes during respiratory infections. This depression is often selective, one enzyme being present in normal amounts whilst the other two show lowered values or are absent (Hess, 1913; Davison, 1925; Farber, Schwachman and Maddock, 1943; McDougall, 1950). This demonstrates the need to examine the activity of all three pancreatic enzymes in the duodenal juice in suspicious cases and not to rely merely on a trypsin estimation as is the procedure in many centres. McDougall (1950) reported normal enzyme activity in 18 children with

severe malnutrition. She did not report on the serum protein patterns but Gomez *et al.* (1954) and Mukherjee and Werner (1954), both working with infants with protein malnutrition, correlated the level of pancreatic enzyme activity with the serum albumin level. Gomez *et al.* noted no correlation, but Mukherjee and Werner found a significant correlation between amylase activity and serum albumin, and at albumin levels below 2.5 g.% a linear regression existed between the two. The bulk of evidence suggests that pancreatic exocrine function may be depressed in a variety of chronic nutritional disturbances in infancy, especially if these are associated with alimentary or respiratory infections. Such pancreatic depression is less likely to occur in acute disorders of sudden onset. Matsaniotis (1957) criticized the use of amino-acid curves after a protein meal as a test for pancreatic function because abnormally low values were not necessarily due to diminished output of pancreatic enzymes but might reflect impaired absorption or abnormal rates of amino-acid uptake by the tissues. In a series of infants with simple inanition he found normal absorption after a meal of casein hydrolysate, and normal removal rates of amino-acid from the blood after intravenous hydrolysates. As a result of this work he stated that the proteolytic activity in the gastro-intestinal tract of infants with this type of undernutrition was not impaired.

The infants in the present series had evidence of chronic protein deficiency as shown by depression of the serum albumin, muscular wasting and recovery on a high protein diet. Prolonged inadequacy of the diet from whatever cause must lead to lowered protein intake, and this in turn is responsible for diminished output of proteolytic enzymes and thus available dietary protein becomes even less adequate. Confirmatory evidence that these infants were protein-deficient lay in the fact that the serum protein patterns remained abnormal until satisfactory weight gains had been made. This often took several weeks of high protein feeding. Platt (1958) demonstrated clearly the difference in the clinical picture in cases of protein malnutrition with a high carbohydrate intake where the picture of kwashiorkor is seen, and in cases where protein deficiency accompanies a low carbohydrate intake and a marasmic type of malnutrition results. The type of malnutrition seen in this series and in most cases in this country does not lead to florid clinical signs and for this reason often passes unrecognized; a symptomatic diagnosis of chronic gastro-intestinal disorder is applied and the progress is slow and unsatisfactory. The serum protein pattern shows non-specific changes in these disorders and the level

of serum albumin does not bear a direct relationship to the pancreatic enzyme activity, though in general the most severely affected infants showed the lowest levels.

Summary

The serum protein pattern in 20 normal infants and in 47 infants with nutritional disturbances was examined by paper electrophoresis. The albumin fraction was significantly lower than normal in all the infants who had failed to thrive regardless of the aetiology of their condition. The alpha and gamma globulins tended to be higher than normal, the beta globulin and total protein showed no change. The group of infants with chronic diarrhoea showed the most pronounced changes in the protein pattern and also the most severe loss of weight. This group also had the most marked depression of pancreatic function but no definite correlation between serum albumin, percentage of expected weight or titre of duodenal trypsin could be established. The serum protein pattern is of no help in specific diagnosis in infants who fail to thrive, the changes being non-specific.

I wish to thank Professor E. M. Killick for her helpful criticism, Dr. Ursula James for permission to investigate her patients, and both her and Dr. John Bate for permission to include their data on pancreatic function. This work was supported by the Endowment Fund of the Royal Free Hospital and formed part of a thesis accepted for the degree of Ph.D. in the University of London.

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EFFECT OF TRIIODOTHYROACETIC ACID ON THE ELECTROCARDIOGRAM IN CRETINISM

BY

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The purpose of this note is to report the effect of the acetic acid derivative of triiodothyronine (Triac) on the electrocardiogram (E.C.G.) in cretinism. It is well recognized that myxoedema in the adult and cretinism in the infant lead to an abnormal E.C.G. characterized by a low voltage curve, particularly affecting the T waves, and prolongation of the Q-T interval. On treatment with thyroid these changes disappear. Evans (1956) writes that the E.C.G. becomes normal after three weeks' therapy and that 'the adequate dosage of thyroid may be estimated from watching it reinstate and maintain a normal cardiogram'.

1-3: 5: 3-Triiodothyroacetic acid has an immediate effect on the basal metabolic rate and body temperature in hypophysectomized rats (Donhoffer, Várnai and Sziebert-Horváth, 1958). It has a rapid effect on the basal metabolic rate in myxoedema (Trotter, 1955). Ibbertson, Fraser and Alldis (1959) have shown that it causes a rapid change towards normal in the E.C.G. of adults with myxoedema. They also state that 'in a 5-month-old cretin, at eight hours after 0.5 mg. of triac by mouth, there was an obvious increase in the R and T waves of the E.C.G.'. The effect on the E.C.G. in two infants with cretinism is recorded in this paper.

Case Reports

Case 1. This boy was seen at the age of 12 weeks. He was the second child of a Rh positive mother, the other child being a boy aged 16 months who was alive and well, and had no jaundice at birth. The mother had an antepartum haemorrhage one month before delivery. The baby was born three weeks before the expected date of delivery with a birth weight of 4 lb. 13 oz. He was breast fed for four weeks and then fed on Ostermilk. The baby had been slightly jaundiced since the second or third day of life, but the stools had always been rather light yellow in colour. The urine had always been dark.

On examination the baby had a rather harsh cry, moderate jaundice of the skin and conjunctivae, an umbilical hernia, and small right and left inguinal herniae. The liver was palpable two finger breadths below the costal margin and the tip of the spleen was palpable. The skin was rather dry, scaly and greasy, especially over the face, and the tongue protruded (Fig. 1). Blood pressure was 70 mm. systolic by the flush method.

The child weighed 10 lb. 3 oz. (4.625 kg.), length 21 in. (53.3 cm.).

Haemoglobin was 12 gm.%, reticulocytes 4%.

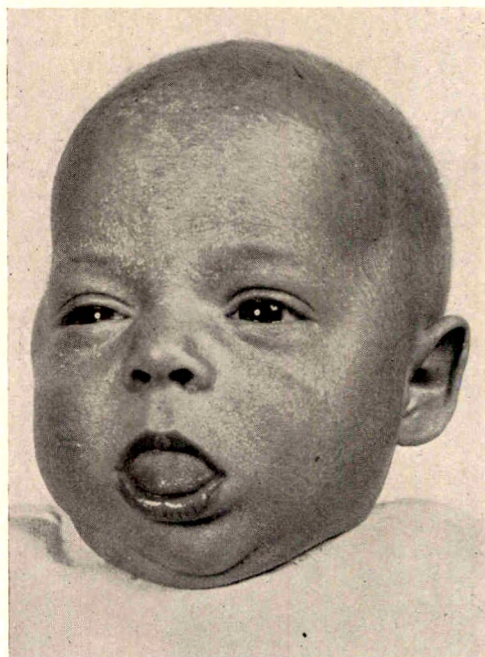


FIG. 1.—Case 1.

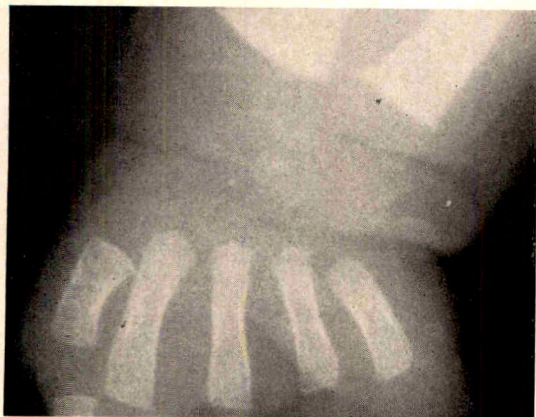


FIG. 2.—Case 1, aged 12 weeks. Radiograph of wrist.

Case 1

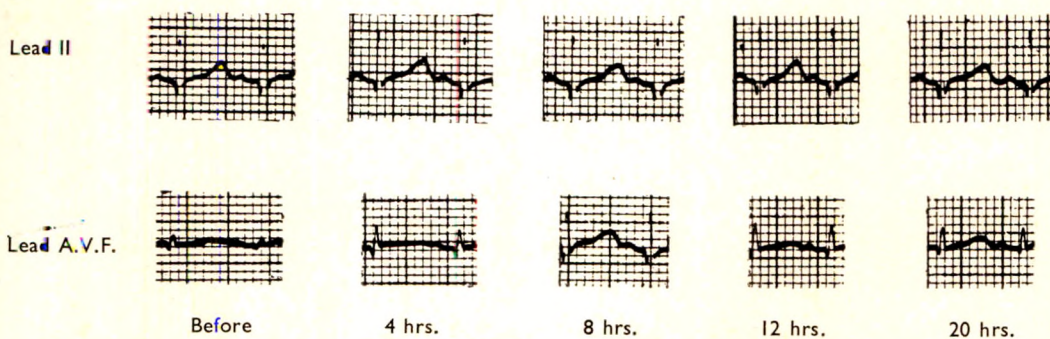


FIG. 3.—Case 1. E.C.G.s before and after Triac (1 mg. given two-hourly for four doses). Timings are in hours after first dose.

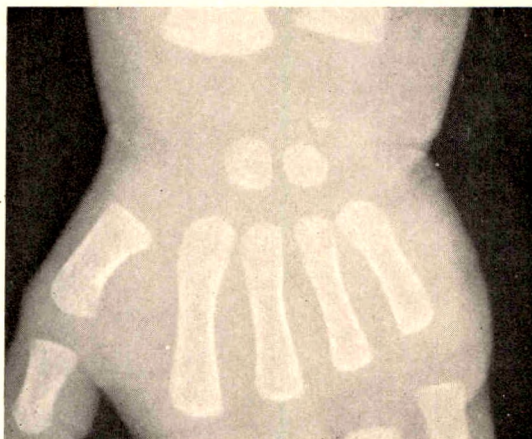


FIG. 4.—Case 1, aged 12 months. Radiograph of wrist.

Radiographs showed a retarded bone age (Fig. 2) and a poorly formed first lumbar vertebra.

The clinical diagnosis of cretinism was clear.

Triac was given in 1-mg. doses at two-hourly intervals for four doses. E.C.G.s were recorded before and after, the timings being given from the time of the first dose (Fig. 3).

Response to treatment with thyroid extract B.P. confirmed the diagnosis of cretinism, clinical and radiological (Fig. 4), progress being normal during the following year.

Case 2. This girl was first seen at the age of 6 months. She was the first child, born at full term after a normal pregnancy, the birth weight being 6 lb. 12 oz. From the age of 4½ months she was noticed to be sluggish, sleeping excessively and not to be making progress. On examination she was an obvious cretin (Fig. 5). Radiographs showed a retarded bone age and poor development of the upper part of the body of the second lumbar vertebra (Fig. 6).

This patient was given 4 mg. Triac in one dose. E.C.G.s were recorded before and after the test dose (Fig. 7).



FIG. 5.—Case 2.



FIG. 6.—Case 2, aged 6 months. Lateral radiograph of lumbar spine.

Response to treatment with thyroid extract B.P. confirmed the diagnosis of cretinism and progress over the next six months was normal.

Normal Infants. A 4-mg. dose of Triac has been given to each of three infants with no endocrine disorder

and a normal E.C.G. pattern. Small variations in the magnitude of the complexes were found on successive recordings even when great care was taken over standardization. There were, however, no changes in voltage comparable in magnitude to that observed in Case 2 described above.

Case 2

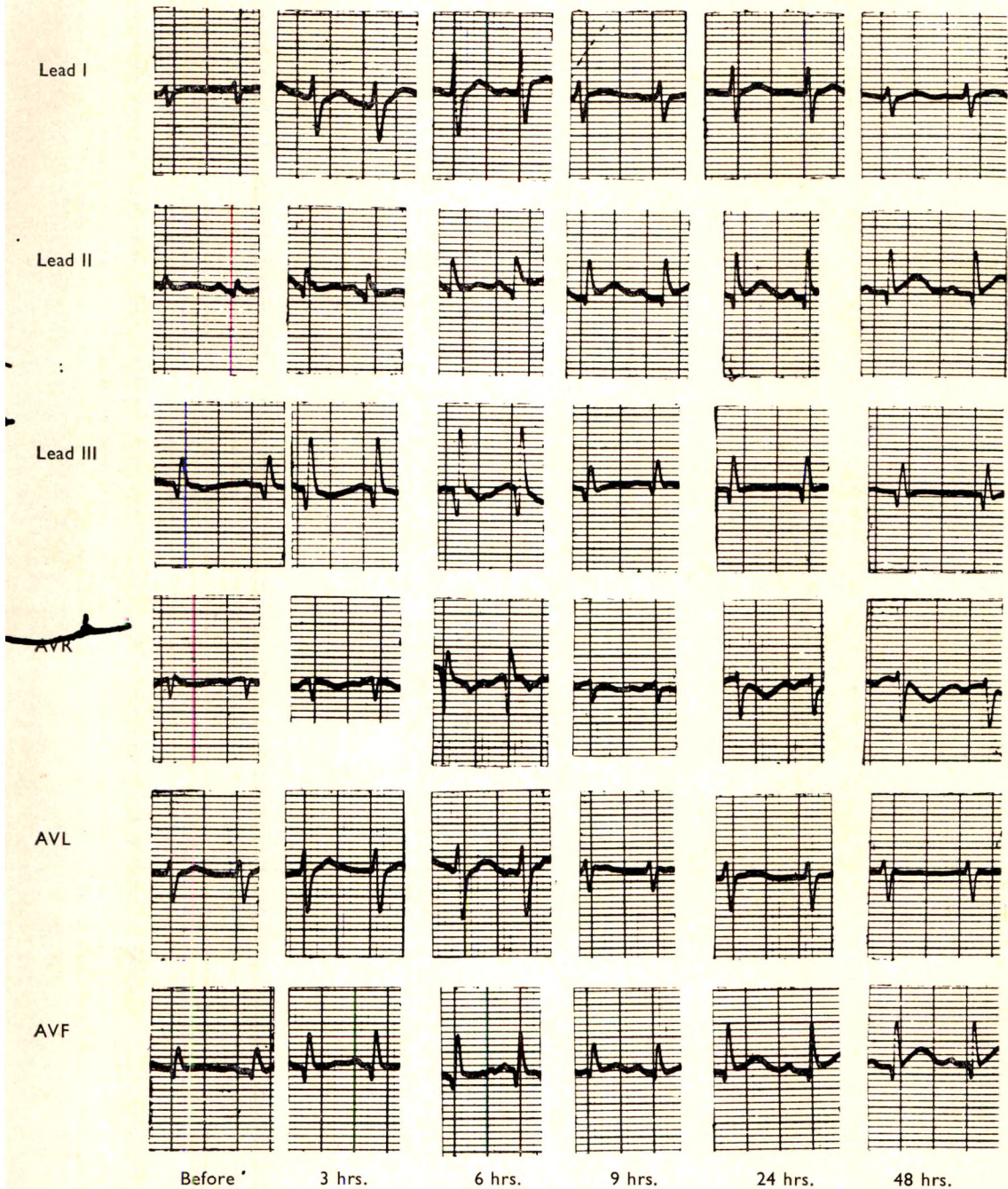


FIG. 7.—Case 2. E.C.G.s before and after Triac (4 mg. given in one dose). Timings are in hours after administration of Triac.

Comment

Care was taken to ensure that the standardization of the E.C.G. machine* was correct and similar for each tracing. The main change noted in the E.C.G.s of cretins was an increase in the voltage. The response was not as marked in the first patient, to whom the triiodothyroacetic acid was given in divided doses over a six-hour period, as in the second patient, to whom a large single dose was given. In the latter case the response was unequivocal; the E.C.G. did not return completely to its previous low voltage pattern even after three days. Whether this test will be of significant value in the diagnosis of less obvious cases of cretinism is doubtful since in them the initial electrocardiogram will often not be significantly abnormal.

* Cambridge Electrite Model Portable Electrocardiograph.

Summary

The effect of triiodothyroacetic acid on the electrocardiogram in cretinism is described.

We are grateful to Professor Russell Fraser for his comments and for the supply of Triac given to the first patient, and to Dr. A. Generowicz for the recordings on the infants with no endocrine disorder.

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IRON-DEFICIENCY ANAEMIA BETWEEN 3 MONTHS AND 2 YEARS OF AGE AND A COMPARISON OF TREATMENT WITH FERROUS SULPHATE AND FERROUS FUMARATE

BY

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A recent paper from this hospital (Morrison, Bass, Davis, Hobson, Madsen and Masters, 1957) reported that about one half of the children under 2 years of age admitted because of acute respiratory infections had haemoglobin concentrations below 11 g. per 100 ml. The purposes of the present investigation were to determine the distribution of the haemoglobin levels in children between 3 months and 2 years of age attending the hospital, to compare two forms of iron treatment and to observe whether infection influenced the response to therapy.

For many years ferrous sulphate (iron content about 33% of exsiccated salt) has been the compound most widely prescribed for the treatment of iron deficiency anaemia. In a small number of patients this causes gastro-intestinal disturbance. The claim has been made that organic compounds of iron are better tolerated. Recently ferrous fumarate, a compound with the empirical formula $\text{FeC}_4\text{H}_2\text{O}_4$, has been advocated (*Lancet*, 1958). The iron content of ferrous fumarate (about 33% iron) is higher than that of ferrous gluconate (about 12% iron) or ferrous succinate (about 25% iron).

Selection of Patients

It was intended to include in the survey of haemoglobin levels the values found in all children between 3 months and 2 years of age attending the casualty department with a new complaint or admitted to the medical ward between January 19, 1958 and March 31, 1958. Owing to the large number of children who attended the casualty department, pressure of work made it necessary to include casualty attendances during the morning only for much of the period. One hundred and three children attending the casualty department and 53 admitted to the medical ward were included in the survey. Seventy-

three children with haemoglobin levels below 11 g. per 100 ml. were observed in the assessment of therapy. Forty-seven of these children were initially seen in the survey and 26 after the survey period ended.

Methods

Approximately 0.4 ml. of capillary blood was collected from each patient into a Pasteur pipette containing dried heparin. The sample was ejected into a small tube, well mixed and immediately used to fill pipettes for estimation of haemoglobin, packed cell volume and erythrocyte sedimentation rate (E.S.R.). The haemoglobin was estimated by the oxyhaemoglobin method described by Dacie (1956). An Ilford 0.5 neutral density screen was read with each series of estimations. Its equivalent haemoglobin value was determined by using blood of known haemoglobin content supplied by Messrs. Keeler Ltd. Each pipette was calibrated. The packed cell volume (P.C.V.) was estimated using capillary tubes spun in a Hawksley microhaematocrit centrifuge at 12,000 g. for five minutes. The E.S.R. was estimated using a tube of 1.5 mm. bore and a column of blood 100 mm. long.

Three mixtures (A, B and C) were prepared; none of the medical staff knew which was issued to a particular child, the records being kept by the pharmacist:

- Ferrous fumarate in a flavoured suspension containing 75 mg. (equivalent to 25 mg. elemental iron) per 4 ml.
- Ferrous sulphate in a flavoured vehicle similar to that used for Ferrous Sulphate Mixture for infants (British National Formulary, 1957) modified to contain 120 mg. hydrated salt (equivalent to 25 mg. elemental iron) per 4 ml.
- A placebo consisting of the flavoured vehicle without ferrous sulphate.

The placebo was given to every third child with a haemoglobin level between 9 and 11 g. per 100 ml. presenting in four consecutive weeks of the study in order to have a control group for comparison of side-effects and

spontaneous haemoglobin changes. It was not felt wise to give the placebo to children with a haemoglobin level below 9 g. per 100 ml.

In order to ensure comparability as regards haemoglobin levels and age in the children given ferrous sulphate and ferrous fumarate, the children were allotted to one of four groups:

3 months-1 year	}	haemoglobin 9-11 g. per 100 ml.
1 year-2 years		
3 months-1 year	}	haemoglobin under 9 g. per 100 ml.
1 year-2 years		

The mixtures were given in rotation to the patients in each group according to the order of arrival of the prescriptions in the pharmacy.

All mixtures were issued with plastic measuring spoons (4 ml. capacity) and the following instructions:

'One teaspoonful after food once a day for 3 days, twice a day for the next 3 days, then three times a day.'

The mother was asked to bring the child back two weeks and four weeks after the start of treatment. On the first return visit she was given another bottle of the same medicine. On each visit the doctor reassessed the child's condition and asked whether any vomiting, diarrhoea or constipation had occurred since the previous visit. Any comments provided by the mother about the child's reaction to the medicine were noted.

Results

Haemoglobin Levels. Fig. 1 shows the total number of children with haemoglobin levels in each one-gramme range. There is a skew distribution in which 20% of the children have haemoglobin levels

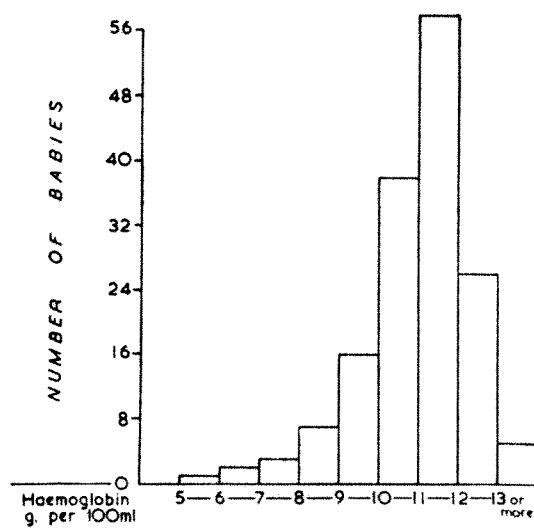


FIG. 1.

of 12 g. per 100 ml. or more, 37% have between 11 and 12 g. per 100 ml. and 43% have under 11 g. per 100 ml. Of the children requiring admission to the medical ward, 53% had haemoglobin levels below 11 g. per 100 ml., a finding similar to that of Morrison *et al.* (1957).

Table 1 gives the averages of the mean corpuscular

TABLE 1
CORRELATION OF MEAN CORPUSCULAR HAEMOGLOBIN CONCENTRATIONS WITH HAEMOGLOBIN LEVELS

Haemoglobin range (g. per 100 ml.)	Under 9	9-10	10-11	11-12	12 or more
Mean M.C.H.C. (%)	27.1	30.2	31.2	32.4	32.5
No. of patients	13	15	38	56	27

haemoglobin concentrations (M.C.H.C.) of the children in each one-gramme range of haemoglobin level. The progressive reduction in average M.C.H.C. in the lower haemoglobin ranges indicates an iron-deficiency factor.

Table 2 gives the average E.S.R. of the children in

TABLE 2
CORRELATION OF ERYTHROCYTE SEDIMENTATION RATES WITH HAEMOGLOBIN LEVELS

Haemoglobin range (g. per 100 ml.)	Under 9	9-10	10-11	11-12	12 or more
Mean E.S.R. (mm./hr.)	30	29	20	16	13
No. of patients*	13	16	38	58	31

* The numbers of patients are different from those in Table 1 as the M.C.H.C. was not determined in every patient in whom an E.S.R. was observed and who was included in the survey.

each one-gramme range of haemoglobin level. There is a rise in average E.S.R. from the highest haemoglobin range downwards. Iron deficiency anaemia alone may not cause a rise in the E.S.R. (Terry, 1950); several children in the survey with haemoglobin levels below 9 g. per 100 ml. had E.S.R.s of less than 10 mm. in one hour.

Assessment of Iron Therapy. Table 3 shows the acceptability of the three medicines (A, B and C). Only about one third as many children received the placebo as received either of the iron mixtures. A liking for the medicine was remarked by the mothers in a majority of children receiving the placebo and only in a few of the children receiving the iron mixtures. A distaste for the medicine was confined to the children receiving the iron mixtures and was slightly more frequent in children receiving

TABLE 3
COMPARISON OF ACCEPTABILITY OF MEDICINES

	Ferrous Fumarate	Ferrous Sulphate	Placebo
Totals allocated to treatment group*	31	31	11
Number returning once	24	27	9
Number returning twice	22	22	7
Number liking medicine	3	4	5
Number disliking medicine	4	10	0
Vomiting	1	0	0
Diarrhoea	1	0	1
Constipation	3	4	2

* Includes nine babies who did not complete their course of medicine.

ferrous sulphate. Vomiting, diarrhoea or constipation were noted in only a small proportion of children. A comparison of their incidence in the iron-treated groups and placebo group reveals no evidence that these symptoms were related to the administration of either iron mixture. There were no other symptoms attributable to the iron mixtures.

Table 4 compares the haemoglobin responses to

TABLE 4
COMPARISON OF HAEMOGLOBIN RESPONSE TO EACH MEDICINE IN PATIENTS WITH INITIAL HAEMOGLOBIN LEVELS BETWEEN 9 AND 11 g. PER 100 ml.

	Mean Haemoglobin (g. per 100 ml.)		
	Ferrous Fumarate	Ferrous Sulphate	Placebo
Initially	10.1*	10.0*	10.3*
After 2 weeks	10.8	11.0	10.6
After 4 weeks	11.5	11.3	10.7
Rise after 4 weeks	1.4	1.3	0.4
Number of patients	14	15	7

* There is no significant difference between the initial haemoglobin levels in the groups receiving iron therapy and the placebo group ($p > 0.10$). The mean change in haemoglobin level of those children receiving either type of iron therapy is significantly greater than of those receiving the placebo ($p < 0.01$).

the three medicines in the slightly anaemic children. The mean responses to the two iron mixtures were almost equal and considerably more than the change occurring in the group receiving the placebo.

Table 5 compares the haemoglobin and M.C.H.C.

TABLE 5
COMPARISON OF HAEMOGLOBIN AND M.C.H.C. RESPONSE TO EACH MEDICINE IN PATIENTS WITH INITIAL HAEMOGLOBIN LEVELS BELOW 9 g. PER 100 ml.

	Mean Haemoglobin (g. per 100 ml.)		Mean M.C.H.C. (%)	
	Ferrous Fumarate	Ferrous Sulphate	Ferrous Fumarate	Ferrous Sulphate
Initially	6.8	8.0	25.8	27.5
After 2 weeks	8.7	9.6	26.4	27.5
After 4 weeks	10.4	10.4	27.5	29.4
Rise	3.6	2.4	1.7	1.9
No. of patients	8	7	7	7

responses to the two iron mixtures in the children with initial haemoglobin levels below 9 g. per 100 ml. There was a good response to both iron mixtures. As would be expected, the response to iron therapy is greater when the haemoglobin level is lower. The response is noticeable even when the initial haemoglobin level is between 10 and 11 g. per 100 ml., the average rise in these patients being just over 1 g. per 100 ml.

Table 6 is an attempt to assess whether the infections found in the slightly anaemic children and the course they took influenced the response to iron therapy. It can be seen that there was no substantial difference between the haemoglobin responses in the groups selected on the basis of E.S.R. patterns.

Summary

Anaemia is still a common finding in young children attending this hospital. The anaemia

TABLE 6
CORRELATION OF E.S.R. LEVELS WITH RESPONSE TO IRON THERAPY IN BABIES WITH HAEMOGLOBIN LEVELS INITIALLY 9-11 g. PER 100 ml.

No. of Babies	Description	E.S.R. Group*			Response to Iron Therapy			
		Mean E.S.R. Values (mm.)			Mean Haemoglobin (g. per 100 ml.)			
		Initial	2 weeks	4 weeks	Initial	2 weeks	4 weeks	Mean Rise
9	All E.S.R.s under 15 mm./hr.	3	7	6	10.2	10.8	11.8	1.6
11	Final E.S.R. at least 15 mm./hr. less than initial E.S.R.	41	18	13	10.0	11.0	11.2	1.2
8	Remainder	17	13	19	9.7	10.4	10.9	1.2

* If a high E.S.R. is taken to indicate infection and a fall improvement of infection, the first group would be babies with slight infection, the second with an improving infection and the third with continuing infection.

usually responds to oral iron therapy, whether given as a ferrous sulphate or a ferrous fumarate mixture, both being generally palatable. The presence of a persistently raised E.S.R. (an indication of infection) is not associated with a substantial reduction in the response to iron therapy.

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THE SIGNIFICANCE OF ONE UMBILICAL ARTERY

BY

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(RECEIVED FOR PUBLICATION JULY 13, 1959)

Absence of one umbilical artery is a rare finding, usually associated with other severe congenital malformations. The earliest recorded case is attributed to Casp. Bauhin in 1621, although Noortwyck (1743) quotes Vesalius' description '*unam tantum arteriam in fune Fallopius vidit*'. Otto (1830) collected 41 case reports from the literature, and Hyrtl (1870) described 14 cases of his own and found 16 more in the literature. Browne (1925) referred to one case with a single artery and numerous capillaries replacing the vein. Benirschke and Brown (1955) described 55 cases, and Richart and Benirschke (1958) described one further case with gonadal dysgenesis. Javert and Barton (1952) examined the umbilical cord of 297 aborted foetuses of four months' gestation and found one with a single artery. Of the 182 cases of symphodia collected by Ballantyne (1898), Kampmeier (1927) and Hendry and Kohler (1956), 95 had a single artery in the umbilical cord, and in the remainder the cord was not examined. Schatz (1900) found 11 cases among 46 acardiac monovular twins and three acardiac monovular triplets. There is therefore clearly a high incidence in acardiac foetuses and symphodia. In foetuses without acardia or symphodia the incidence appears to be relatively low, and only Javert and Barton (1952) provide data from which an assessment can be made.

This paper describes 11 cases encountered among routine autopsies performed at the Birmingham Children's Hospital from March, 1958, to February, 1959, in autopsies on 159 stillbirths and 252 live born babies of 8 weeks of age or less. Severe malformations were found in nine (81%) and in 23% of the controls.

Case Reports

Case 1. A female baby was stillborn at 36 weeks' gestation to a para 1 mother aged 20. There had been a threatened abortion at 3 months.

Autopsy showed rotation of the trunk through 90° so that the buttocks were facing the left side, and a large hernia into the body stalk. The sac was formed by

amnion and contained liver and loops of bowel. The lungs were hypoplastic and abnormally lobed. The heart showed a defect in the membranous part of the ventricular septum. The right renal artery arose from the proximal part of the superior mesenteric artery. The umbilical artery entered the right internal iliac artery and was wider than normal. The small intestine was short (97 cm.) and was strangulated distally in the hernial sac. The brain showed bilateral cirroid aneurysms of the Sylvian fissures with focal microgyria and encephalomalacia of the underlying cerebral tissue on the right side. The placenta weighed 237 g. and was normal. The umbilical cord lay in the wall of the hernial sac and was short (14.5 cm.). It contained one artery and one vein throughout its length.

Case 2. A male baby was born at full term after a normal pregnancy. On the third day he had a surgical repair for oesophageal atresia with tracheal fistula and died six days later with respiratory obstruction and infection.

Autopsy showed repair of the tracheo-oesophageal fistula with oesophageal anastomosis. There was a diaphragmatic urethral valve at 0.9 cm. from the bladder neck. The bladder was dilated and hypertrophied and there was bilateral hydronephrosis and hydroureter. The right umbilical artery was absent and the right common iliac artery was narrow.

Case 3. A male infant was born at full term after a difficult delivery and died six hours later. The antenatal history was not known.

At autopsy there was gross radial deviation of the left thumb and radius. The small intestine was incompletely rotated and unfixed, and there was a Meckel's diverticulum. The right kidney and ureter were absent. The left kidney had two cortical cysts and the renal pelvis and ureter were dilated. The bladder was grossly dilated and hypertrophied and filled with heavily blood-stained fluid. There were lacerations of the bladder wall 2.5 and 3 cm. in length. The internal urethral orifice was stenotic and partially valved by mucous membrane, and beyond it the urethra was atretic. The testes were intra-abdominal and normal. The right renal artery was absent, and there were two left renal arteries. The left common iliac vessels were small, and the left umbilical artery was absent.

Case 4. A female baby was born at 35 weeks' gestation to a gravida 3 mother after a normal pregnancy. The baby died after one hour.

Autopsy showed low set ears and bilateral pes cavus. The external genitalia were abnormal, the main feature resembling a scrotum with a median dimple on its anterior surface. On either side of the scrotum were two folds resembling labia. The anus was represented by a shallow depression. There was oesophageal atresia, tracheo-oesophageal fistula and atresia of the duodenum. The small intestine showed a Meckel's diverticulum and lack of mesenteric fixation. The colon ended blindly on the posterior wall of the bladder. The liver showed abnormal lobulation of its inferior surface. The gall bladder was absent. The larynx and left bronchus were atretic and the left lung was absent. The heart had a high ventricular septal defect and a common truncus. There were two renal arteries on each side. The right umbilical artery was absent, and the right common iliac artery was smaller than the left. There was a persistent left superior vena cava. Both kidneys were small and cystic. There was duplication of the right ureter and renal pelvis. The two ureters were thin cords uniting caudally and ending blindly in the bladder wall. The left ureter and ureteric orifice were moderately dilated. The bladder was grossly dilated and hypertrophied. The internal urethral orifice was stenotic, and from it a hypoplastic urethra passed to the scrotal dimple. There were two normal ovaries but no uterus nor vagina.

Case 5. A male baby was stillborn at 31 weeks to a primigravida mother aged 20. The antenatal history was not known.

Autopsy showed coarse facial features with a depressed nasal bridge and low-set ears. There was a left diaphragmatic hernia, and the left pleural cavity was also continuous with the pericardial cavity. The heart showed atresia of the tricuspid valve and pulmonary infundibulum. The right ventricle was a minute blind chamber. There was a large atrial septal defect. The pulmonary arteries and ductus arteriosus were hypoplastic. The left umbilical artery was absent and the left common iliac artery was narrow. The right kidney and ureter were absent. The left kidney was hypoplastic and cystic. The left ureter was a thin cord with a normal ureteric orifice. The bladder was much dilated and hypertrophied. There was stenosis of the bladder neck, atresia of the prostatic urethra and agenesis of the prostate. The testes were intra-abdominal and normal. The lower end of the colon was atretic, ending blindly on the bladder wall. The termination of the spinal cord was abnormal. The cord extended to the lower end of the sacral canal and passed into a small skin-covered cartilaginous peg on its external aspect.

The placenta weighed 240 g. and was normal. The umbilical cord was normal apart from absence of one artery.

Case 6. A female baby was born at 36 weeks to a para 1 mother aged 17. The delivery was normal but the baby had white asphyxia and died after eight hours.

At autopsy the ears were low-set and the external genitalia were abnormal, represented by a median mound of soft tissue covered by skin. There was a sinus at the junction of the anus and the perineal skin. There was bilateral renal hypoplasia and agenesis of the bladder. The ureters were dilated to cystic proportions distally, and at the lower end of the uterus they communicated with the vagina which was continuous with the perianal sinus. The uterus was bicornuate, the ovaries were normal. The right umbilical artery was absent, and the right common iliac artery was very small. The lower part of the left umbilical artery gave rise to a vessel which crossed over to the right and divided into the right external and internal iliac arteries.

The placenta weighed 606 g. and was normal. The cord was excessively long (83 cm.).

Case 7. The first of monovular male twins was stillborn at 32 weeks to a para 1 mother, aged 25, after prolapse of the cord. The antenatal history was normal. The second twin died after 56 hours and had no malformations.

At autopsy the nose was slightly beaked and the ears were normal in position but had a soft flat helix. The kidneys were enlarged and cystic, fused together and low in position. The renal arteries consisted of several minute vessels arising close to the aortic bifurcation. The two ureters were very narrow and passed to a hypoplastic bladder. The urethra and testicles were normal. There was hypoplasia of the stomach, liver and lungs. The right umbilical artery was absent and the right common iliac was smaller than the left.

There was a diamniotic-mono chorionic placenta weighing 362 g. The umbilical cords were attached near the central double amniotic membrane, one being normal and one having a single artery and vein. There were no demonstrable vascular anastomoses.

Case 8. The second of twins was stillborn at 38 weeks to a para 2 mother aged 22, after a normal pregnancy. The first was a female infant with no malformations who thrived normally.

Autopsy examination showed a sirenomid foetus with a single curved lower limb ending in a foot with three broad digits. The trunk consisted of a featureless mass surmounted by a head process. There was no definable perineum, vertebral column, thorax or abdomen, and no upper limbs. The umbilical cord was attached at the upper end of the trunk. The head process was covered by skin and had two auricular appendages on the right with an adjacent red polypoid process. A smear from the process showed epithelial cells with the chromatin pattern associated with the female sex. Internal examination was not performed.

There was a bulky monochorionic placenta weighing 760 g. One umbilical cord was normal and attached marginally. The other was thinner, contained one artery and one vein, and had a velamentous insertion.

Case 9. A female infant was born at full term to a primigravida mother aged 23, after a normal pregnancy.

At three weeks she developed heart failure, which did not respond to treatment and she died at six weeks.

At autopsy the heart was grossly enlarged. There was hypoplasia of the ascending aorta and the aortic arch with a narrow elongated aortic isthmus and a wide ductus arteriosus. There was a small defect in the upper posterior part of the muscular ventricular septum. The aortic valve was bicuspid. The right umbilical artery was absent and the right common iliac artery was narrow.

Case 10. A male infant was born at 31 weeks gestation after surgical induction of labour. The mother was a primigravida aged 25 with fulminating pre-eclamptic toxæmia. The infant died 10 minutes after birth.

At autopsy there were no congenital malformations. Much amniotic cellular debris was found in the lungs. The placenta was normal. The umbilical cord contained one artery and one vein and was otherwise normal.

Case 11. A male baby was stillborn at 41 weeks to a para 3 mother aged 22. The antenatal history was normal.

Autopsy examination showed a macerated baby with only one umbilical artery but no other congenital malformation. The placenta had a marginal infarct. The umbilical cord was normal apart from absence of one artery.

Discussion

There were 11 cases of single umbilical artery among 411 autopsies, an incidence of 2.7%. There is no comparable perinatal investigation reported in the literature. Javert and Barton (1952) found a much lower incidence in foetuses aborted at four months.

Nine of the 11 babies had severe associated malformations, and in eight the malformations were multiple. This incidence of 81% is comparable with the 76% found by Benirschke and Brown (1955) and much higher than the incidence of 33% recorded by Hyrtl (1870), and the 56% of Otto (1830). There were malformations of the lower urinary tract in seven babies. One was a sirenoïd foetus with no perineal orifices, one had valvular obstruction of the posterior urethra, two had extreme hypoplasia or agenesis of the bladder, and three had atresia or severe stenosis of the bladder neck. In two cases with bladder neck obstruction there was also rectal atresia. There were four cases with renal hypoplasia or agenesis, four cases with malformations of the heart, and two with oesophageal atresia. Ballantyne (1904) stated that the commonest associated malformation was defective development of the bladder and sirenomelia. Benirschke and Brown (1955) found mainly malformations of the heart and central nervous system, while anencephaly was the commonest malformation found by Hyrtl (1870).

There were two monovular twins. In both cases the other twin had two umbilical arteries and no malformations. There was also a high incidence of twinning in Benirschke and Brown's (1955) cases. They found one monovular and four binovular twins, a total incidence of 9%. An abnormal cord was found in each pair. Hyrtl (1870) described female monovular twins (incidence 7%) and male triplets, one foetus in each set having the abnormality. Schatz (1900) found 11 cases in monovular twins and one in a single foetus. In each case only one of the twins had one artery.

There were seven placentas available for examination. One was infarcted and the remainder were normal. One umbilical cord was abnormally long, one was short and a third had a velamentous insertion. Benirschke and Brown (1955) found a high incidence of placental anomalies such as circumvallation, circum-margination, velamentous insertion of the cord and extensive infarction. Ballantyne (1898) stated that the placentas of symphodia tended to show abnormalities of size, shape, consistency and mode of insertion of the cord.

There were equal numbers of live and stillbirths. There was also a high incidence of stillbirths (76%) in Benirschke and Brown's (1955) cases. Hyrtl (1870) found only 7% were stillbirths, but this was probably due to autopsies being infrequently performed on stillbirths.

There were equal numbers of male and female foetuses, and this agrees with the findings of most authors. Kampmeier (1927), however, found a male preponderance in sirenoïds, and Hyrtl found only males in his series of 12 single foetuses.

No correlation was found between the abnormality and maternal factors. Of the mothers 60% were multiparous, and their ages ranged from 17 to 25 years. The pregnancies were normal in seven cases, in one there was a threatened abortion, and in one toxæmia of pregnancy. Benirschke and Brown (1955) had found a high incidence of toxæmia and hydramnios.

The condition can be simply diagnosed at birth by careful examination of the cut surface of the umbilical cord. This is of little practical value in the presence of obvious gross malformations. There were no gross external malformations in six of the cases, however: two of these, Cases 10 and 11, showed no associated malformations at autopsy; two, Cases 5 and 7, had malformations incompatible with life; two, Cases 2 and 9, had malformations which may be amenable to surgical treatment. Therefore a newborn infant without gross malformations visible externally, but with only one umbilical

artery, has a 2:1 risk of severe internal malformations, which may warrant early surgical correction.

Summary

Eleven cases of single umbilical artery are described. They were encountered among 411 autopsies on stillborn and live-born babies under 8 weeks of age. Nine had severe associated congenital malformations involving particularly the urinary tract. Absence of an umbilical artery can be diagnosed by simple examination of the cord at birth. In the absence of severe external malformations such an infant has a 2:1 risk of internal malformations which may require early surgical treatment.

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THE 'STIFF MAN SYNDROME' IN A BOY

BY

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Tetanus is common in Malaya, and the case to be described, although first diagnosed as recurrent tetanus, is put forward as a case of the 'stiff man syndrome' or progressive fluctuating muscular rigidity and spasm.

Case Report

In October, 1958, a Chinese boy, aged 7 years, was transferred to the Children's Unit with a diagnosis of recurrent tetanus. According to the mother, he had been ill intermittently since 1957 when he was first admitted to hospital complaining of stiffness of the body and inability to open his mouth. He apparently recovered from this illness, but was readmitted on two further occasions with similar complaints. For over one year he had been unable to open his mouth properly. Since August, 1958, this difficulty had increased so that taking solid food was impossible and he had been fed on *doctors' only*. From time to time during the past year his face had 'twisted up' (mother's description). His mother had brought him to hospital again because for the last month he had been 'stiff all over' and had been having 'fits'. She was quite certain that he had never had any injury, and that before 1957 he had been quite well. He had never been immunized. There were five other children in the family, all of them well.

He had been in different hospitals three times. On his first admission in February, 1957, he had complained of trismus and stiffness of the back and abdomen. He was treated as a case of tetanus, although there was no history of injury, and he had no typical tetanic spasms whilst in hospital. He was admitted on two further occasions in April, 1957, and January, 1958. Each time his complaint was difficulty in opening his mouth, but rigidity of the abdominal muscles (they were described as 'board-like') was noted on examination. There was no involvement of the arms and legs, and the child was able to walk. In January, 1958, recurrent left facial spasms were noted for the first time.

On each occasion the stiffness disappeared in about three weeks and he was discharged, although the inability to open his mouth remained. No investigations were carried out, and no firm diagnosis was made.

In summary, therefore, since February, 1957, the child had suffered from a recurrent illness involving stiffness of the abdominal muscles, together with difficulty in

opening his mouth. The latter complaint had become permanent and was associated with left facial spasms.

When seen by me in October, 1958, the child was conscious, alert and lying quietly in bed. He lay like a 'wooden soldier' with the head, trunk, arms and legs quite straight. The feet were plantar flexed and the hands were in the *mains d'accoucheur* position. There was a suggestion of risus sardonicus about the mouth, and the muscles of the neck, chest, abdomen and back were tense, clearly outlined, and appeared to be in a state of permanent contraction. There was no opisthotonus although there was marked neck stiffness due to the rigid neck and trunk muscles. The abnormal appearance and

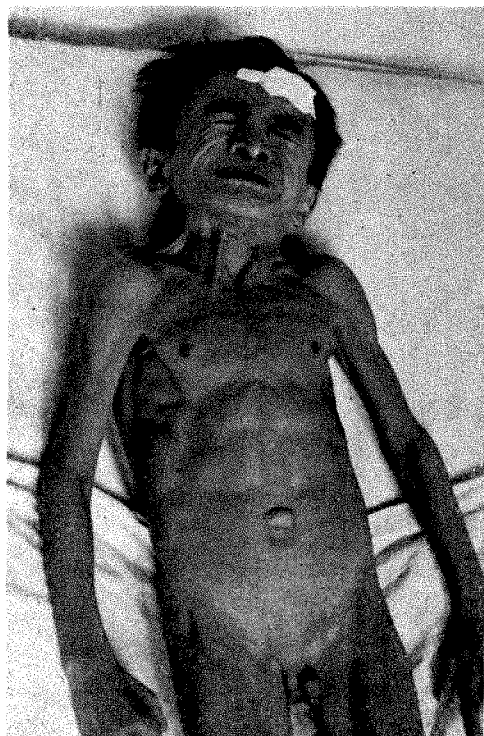


FIG. 1.—Appearance of child during a spasm.

feel of the muscles were absent in the legs and in the forearms.

The child was intelligent and cooperative throughout what appeared to be a most painful physical examination. When at rest he was quiet but when examination was attempted there were violent intermittent spasms of the face and neck muscles. Each spasm lasted about 30 seconds, was accompanied by profuse sweating and appeared to be extremely painful. The similarity to tetanus was marked, although the child was emphatic that the spasms were painless. They were precipitated by efforts to talk, to open the mouth, tapping the face, movements of the arms and legs, and by nursing procedures (Fig. 1).

The other muscles of the body, although remaining rigid, were not involved in the spasms. The child could open his mouth 0.5 cm. only (Fig. 2). It was interesting



FIG. 2.—Demonstrating inability of child to open mouth.

to note that the feel of the edge of the masseter muscles, which is so characteristic in tetanus, was absent in this child. Neither was any jaw jerk obtained. The child was unable to sit, turn in bed, or to stand. When he was supported on his feet there was an immediate increase in the rigidity of all muscles, including the limbs, together with the most violent spasms of the face and neck. The muscles of the trunk were hard and unyielding, and the abdomen was board-like. The feet became strongly plantar flexed. The child remained stiff and straight when lifted from the bed (Fig. 3) but could be 'bent' into a sitting position.

Passive movements of the limbs showed some 'lead pipe' rigidity greater in the legs than in the arms. Active movements were carried out slowly, and power and coordination were poor, being limited by the stiffness. There was no weakness nor wasting of any particular

muscle group, and there were no involuntary movements (apart from the spasms), tremors, or muscle fibrillation. The limb reflexes were normal and there were no sensory abnormalities. During sleep the child was relaxed and the muscles were quite soft. Examination of the heart and lungs revealed nothing remarkable.

The child remained in hospital for 30 days during which time the stiffness and rigidity of the muscles slowly regressed, regression being uniform throughout the affected muscles. The spasms became less violent and frequent and there was some improvement in his ability to open his mouth. Two weeks after admission the child was able to walk, but with a wooden stiff-legged gait. If he lost his balance he fell forward completely stiffly. At no time during his stay did he complain of any muscular pain. Apart from a high protein diet enriched with vitamins he received no specific treatment.

At the time of his discharge he was fairly active. There was no stiffness nor tenseness of the muscles. The spasms had ceased and he could open his mouth 1.5 cm. He disliked trying to run because he said his legs felt heavy. Since discharge he has been seen regularly and has remained almost free from symptoms. He is still unable to open his mouth fully and he dislikes running. His mother says that occasionally his face 'twists up'.



FIG. 3.—Demonstrating overall rigidity of child when lifted.

Whilst in hospital he was investigated in detail. Blood biochemistry was normal (Na; K; Ca; CO₂ combining power; inorganic phosphate; plasma proteins; blood urea). A four-hour glucose tolerance test with simultaneous phosphate estimations was normal. Liver function tests were normal, cerebrospinal fluid examination was normal, as was the electrocardiograph. Radiographs of the skull and temporo-mandibular joints showed no lesion to account for his inability to open his mouth. The urine was tested repeatedly for reducing substances but they were absent on all occasions. Muscle biopsy was not performed.

Discussion

For want of a more accurate term the stiff man syndrome has been used to describe this case.

Moersch and Woltman (1956), who first described the condition, labelled it more accurately progressive fluctuating muscular rigidity and spasm. They record having seen 14 cases (all adults) in 32 years. In the case they described in detail there was episodic tightening of the muscles of the neck, which gradually increased in frequency, duration and extent. Four years after the onset of the disease the neck muscles were permanently rigid, as were the muscles of the trunk, abdomen and back. The rigidity was punctuated by moderately painful spasms, which were precipitated by a sudden jar or voluntary movement. Twelve years after the onset of the symptoms he still had the muscle rigidity and the spasms. Of the other 13 cases summarized, stiffness, rigidity or tightness was the chief initial complaint. All cases had experienced spasms, but these were not always painful or marked. Ten of the cases had a gradual onset and the muscles of the neck or trunk and shoulder were first affected. In all cases the stiffness spread to other muscles. Involvement of the hands and feet was minor, and the face was not involved in any case. In no case was there any mental deterioration. The cases were followed up from three to 14 years, and in all except one there was a gradual increase in the disability. All cases were notable for the complete lack of other physical signs, the failure of investigations to reveal any abnormality and the failure of all treatment to influence the course of the disease. Asher (1958) and Price and Allott (1958) describe adult cases of this syndrome. In both cases, however, the descriptions differed from Moersch in that the feet and legs were heavily involved, causing a pronounced talipes equinovarus. In Asher's case there were additional mental changes. Similarly, the present case differed from the description of Moersch in that there was marked involvement of the face, although in other respects the similarity was close.

If this syndrome is to be admitted as an entity, therefore, it seems that any group of muscles may be involved initially and that the course of the disease is subject to wide variations. The only common factor is the fluctuating rigidity, coupled with an almost complete lack of other abnormal findings, and the failure of all forms of treatment.

Clinically the syndrome resembles recurrent tetanus in many ways. True second attacks of tetanus in the same patient are very rare. I have found only two clear references in the literature (Möbus, 1950; Gunaratna, 1958). Westwater (1917) mentions a case, but as the attack followed a gunshot wound, and as it is not clear whether the case had any surgical treatment, this case may be a recrudescence

due to the persistence of a foreign body. It is surprising that so few cases of true second attacks of tetanus are on record, since a clinical attack of tetanus does not give any immunity to subsequent attacks (Spaeth, 1949). Professor Adams of Durban states that in a series of 360 cases of tetanus he has not seen any true second attack. Chronic recurrent tetanus due to the persistence of a foreign body or focus of infection in the tissues is relatively well known (Mouchet, 1916; Adams, 1958). The clinical picture of tetanus can vary very widely, with few or many muscle groups involved, and with any degree of hypertonus. The tetanic spasms may be absent or present in any degree of severity.

Nevertheless, the picture of the stiff man syndrome, when viewed as a disease process in time, is quite unlike that of tetanus, and on clinical grounds alone it is reasonable to assume that there is no relation between the two conditions.

It has been suggested (Leading article, 1956) that the stiff man syndrome may be due to degenerative changes in the basal ganglia and that the syndrome is a variant of dystonia musculorum deformans. Superficially there are similarities between dystonia and the stiff man syndrome. Wechsler and Brock (1922) described a variant of dystonia in which the involuntary movements were largely absent and in which muscle rigidity was the predominant disability. In both dystonia and the stiff man syndrome muscle stiffness and rigidity, which slowly spreads, is the presenting disability. The end result of both diseases is associated with deformities. In dystonia, however, involuntary movements are a marked feature of the disease and there are often mental changes (Ford, 1952). However, apart from muscle spasm and stiffness, the two syndromes appear to have little in common. Although the present case has not been followed long enough, all the other reported cases showed no clinical evidence of degenerative brain changes.

I have thought it of interest to report this case since, like the cases reported by others, it does not appear to fit any recognizable condition, and so far the syndrome has been reported only in adults.

Summary

A case of the stiff man syndrome or progressive fluctuating muscular rigidity is described. The condition is briefly reviewed.

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Addendum.

Since submitting this paper, a case of recurrent tetanus has occurred at this Hospital, under the care of Mr. S. M. Alhady, details of which will be reported later.

GOUT AND CEREBRAL PALSY IN A THREE-YEAR-OLD BOY

BY

IAN D. RILEY

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(RECEIVED FOR PUBLICATION JULY 6, 1959)

Gout is very uncommon in children, and its appearance in a patient with cerebral palsy does not appear to have been recorded before.

Case Report

A.W. was born on January 20, 1951, at full term after a normal delivery and weighed 7 lb. 6 oz. He was adopted after medical examination aged 1 week. He was slow to sit up, his muscle tone was poor and at 1 year a diagnosis of cerebral palsy was made. In May, 1953, a ganglionic swelling was removed from his left foot which contained amorphous debris on histological examination. He was then showing signs of athetosis, for which physiotherapy was prescribed, and he was sent to a day school for children with cerebral palsy, which he still attends. In the same year he was admitted to hospital for investigation but developed pneumonia, after which the athetosis became more pronounced. In September, 1954, he developed diffuse painful swellings of the fingers and toes. Radiographs of the hands and feet revealed no abnormality and the sedimentation rate was 9 mm./hr. (Westergren). A diagnosis of Still's disease was made and aspirin prescribed. In 1956 he suffered an exacerbation of his symptoms and in 1958, after a period of absence from school on account of pain and restlessness, he was seen with gross swellings of the fingers and toes. These were lilac in colour and studded with white calcareous deposits. The skin was ulcerated in several places and the appearances were those of gout. His blood uric acid at that time was 10.6 mg.% and he was treated with colchicine $\frac{1}{10}$ gr. four times a day. Ten days later his restlessness was much improved and the lesions were less inflamed, but the dose had to be reduced to $\frac{1}{20}$ gr. on account of diarrhoea. This was later augmented with benemid. Shortly afterwards, as a result of infection entering through one of the ulcerated topi, he developed a large abscess in his right forearm which however healed rapidly after incision but left him emaciated and anaemic. He was transfused on account of iron intolerance and the anaemia did not recur. While in hospital his lower lip became severely ulcerated and six teeth were extracted under general anaesthesia. This in turn led to bronchitis from which he recovered. After a seaside holiday he became much better nourished. On September 19, 1958, he developed a severe generalized convulsion from which he recovered rapidly.

At the present time he is a surprisingly contented child with a high grade mental defect. He can speak with difficulty and can assimilate simple teaching. He is very emaciated, weighing only 25 lb. at 7 years (Fig. 1) and he



FIG. 1.—Showing emaciation and characteristic posture. Note bitten lip.

suffers from severe generalized athetosis with extensor spasms. He can neither sit nor stand unaided, grimacing is frequent, speech and swallowing are impaired and he salivates continually. The gout involves both hands and feet (Figs. 2 and 3) and the lobes of the ears. The digits are red and swollen with numerous white uratic deposits, and although partially controlled by treatment exacerbations are frequent. There has been no evidence of a

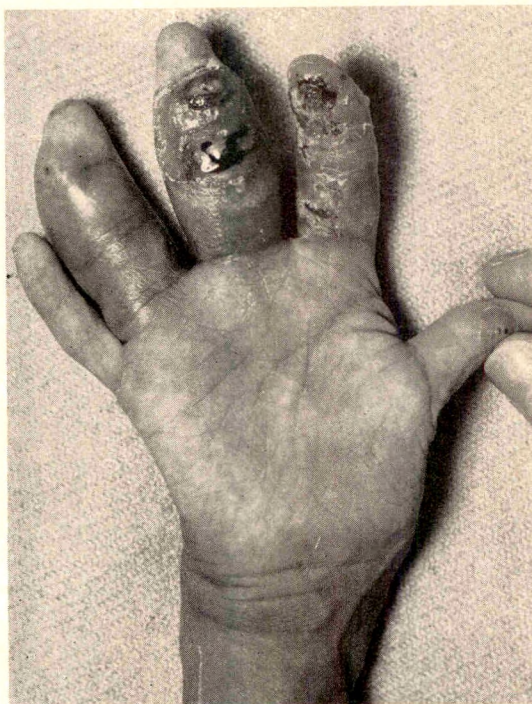


FIG. 2.—Ulcerated gouty lesions of hand.

return of his anaemia and bone marrow examination shows no evidence of leukaemia.

Other laboratory examinations include: 24-hour uric acid output 504 mg.; blood urea 30 mg.%; Mantoux reaction negative. Radiographs show gouty changes in the hands (Fig. 4) and also subluxation of the right hip. Chromatography of the urine shows no abnormality.

Discussion

Gout is very uncommon in childhood. Bernstein (1947), in an excellent historical review, says that Hippocrates, Sydenham and Heberden never saw it and that Hippocrates believes that it did not occur before puberty.

Sydenham, who developed gout at 25, would certainly have remarked on it had he seen it. The first writer to describe it was Morgagni: '*Ipsi puellas vidi qui infanta vix peracta, acerbis articularum doloris, prehensi decumbant*'. The next writer is Gairdner (1854), who says that he had seen an infant on the breast who had a strong family history of gout. Still (1927) and Garrod (1876) also make reference to juvenile cases.



FIG. 3.—Gout and tophi on foot. Also inflamed ganglion.

In modern writings two types of juvenile gout are recognized, a rare, often fulminating type identical with that seen in adults, and a more common form associated with leukaemia or haemolytic anaemia. A further type associated with chronic liver disease has also been described. The first detailed description in a child is that of Mayer von Schopf (1930) in a baby of 5 weeks. This appears to have been of the adult type although it was associated with an anaemia. Death resulted from broncho-pneumonia. Two cases are recorded at 3½ years, one by Vining and Thompson (1934) in a child with leukaemia, and another by Rauch (1950) with symptoms from 3 years. Apart from these cases all the others were observed after the age of 10. The maximum incidence of gout is in the fifth decade, and it declines in frequency in youth and age. Examples of gout in young persons are described by Claiborne (1940) at 17 years, Bernstein (1947) at 12, 14 and two at 16, Berk (1948) at 11 and Flinchum and Powers (1951) at 15, 26 and 25. Gout and leukaemia in a boy of 11 is recorded by Franck (1944), and anaemia and gout are recorded by

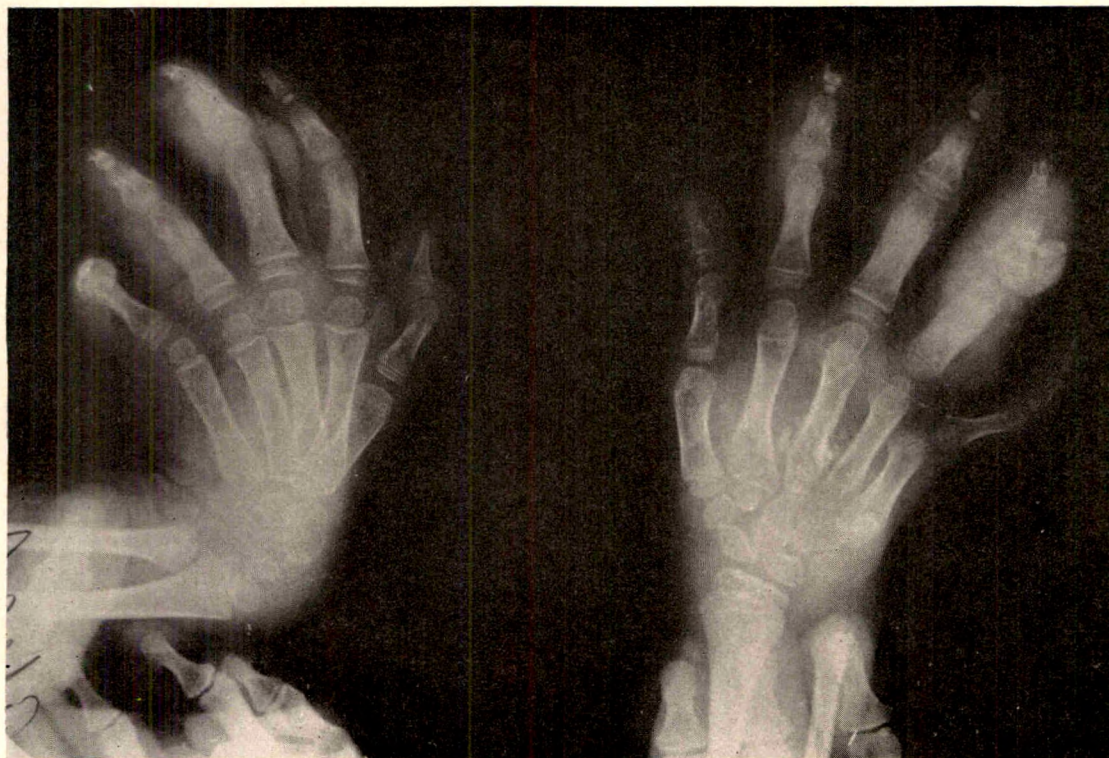


FIG. 4.—Radiograph of hands showing erosions and calcareous deposits.

Nordmann and Höhne (1951) in a child of 12; Morgano and Zino (1953) and Lambie (1940) also report cases. Jeune, Charrat and Bertrand (1957) describe two interesting cases of chronic liver disease associated with a high blood uric acid, one of whom suffered from gout.

No connexion between gout and disease of the central nervous system has been described apart from the degenerative vascular changes which it produces and one case of tophi in the spinal cord causing paraplegia (Koskoff, Morris and Lubic, 1953).

In the present case we believe that the poor general condition of the patient, which resulted from his cerebral palsy, may have aggravated an inherited gouty diathesis and resulted in the premature appearance of symptoms.

Summary

Gout is described in a boy with athetoid cerebral palsy. The disease was first observed at the age of 3 years. No connexion between the two conditions could be established.

The boy remains under the care of Mr. Kenneth Guest, F.R.C.S., and I am much indebted to him for

referring him to me and allowing me to publish this report about him.

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CALCIFICATION OF THE DIGITAL VESSELS IN A CHILD WITH RHEUMATOID ARTHRITIS

BY

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(RECEIVED FOR PUBLICATION JULY 6, 1959)

Calcification of blood vessels occurring during the course of rheumatoid arthritis in a child appears to be unique. It is hoped therefore that this report will be of interest.

Case History

The girl is now 9 years old. Her illness began at the age of 2 years with fever, joint swellings, pericarditis with effusion, rash, splenomegaly, lymphadenopathy and anaemia, indeed the full clinical picture of Still's disease (1897). There was a family history of rheumatic fever on both the paternal and maternal sides but none of rheumatoid arthritis. She was treated along conservative lines in the Royal Hospital for Sick Children, Edinburgh, for one year and then, during her second year there, she was given 20 mg. of A.C.T.H. gel daily for six months followed by 25 mg. of A.C.T.H. gel every second day for six months. Only slight improvement was noted and later it was found that she could be just as well controlled on 50 gr. of aspirin daily. By the time of her discharge home the heart had returned to normal but the joints of all four limbs were still affected and also the cervical spine. She could walk a little with support.

The family moved to Dundee shortly afterwards. One month later, at the age of 4½ years, she was admitted to Dundee Royal Infirmary with a recurrence of pericarditis and widespread acute arthritis. During the ensuing eight months of complete bed-rest, despite such physiotherapy as she could tolerate, the condition of the joints deteriorated. When the pericarditis had resolved, after rather a stormy course with heart failure, the child was transferred to the Children's Orthopaedic Unit so that serial plasters could be made to improve the position of her joints, in which movement was very limited. She was there for five months but again her general condition gave cause for anxiety and she was returned to the paediatric ward.

It was then evident that after three years of active rheumatoid arthritis she had developed amyloid disease. The liver was more than a hand's breadth enlarged and the spleen three fingers' breadths enlarged. There was gross albuminuria (between 600 mg./100 ml. and 1,200 mg./100 ml.) in the 24-hour samples. None of these

findings had been present six months previously. No biopsy was taken as neither the skin nor the lymph nodes were involved, but the Congo red test showed 95% fixation of dye by the tissues in one hour. Although the heart was again clinically normal the arthritis had become even more severe. There was marked dilatation of capillaries at the base of the nails. She could not grasp objects with her hands or move them to her mouth and she could not stand or attempt to walk. Her neck was fixed and her back rigid. Her general condition was poor; she was miserable and suffering a great deal of pain. It was therefore decided to try hormone therapy again. Relatively higher dosage was given on this occasion, namely 20 mg. prednisolone daily for four weeks followed by a gradual reduction to 10 mg. daily. The improvement was striking. Within two months she could feed herself and walk slowly on her own. The B.S.R. fell to normal and remained so for the first time since the onset of her illness. Long term therapy had therefore to be considered.

In order that a check might be kept on the osteoporotic effect of hormone therapy, radiographs were taken of the entire skeleton. These showed gross generalized skeletal decalcification with fusion of the inter-articular processes of the cervical spine and collapse of the fourth to the tenth thoracic vertebrae inclusive (Fig. 1). The lumbar vertebrae were normal. Previous films had shown a normal cervical spine at 3 years but early fusion of the inter-articular processes was present at 4½ years when she was first examined radiologically in Dundee. On neither occasion had a radiograph of the thoracic spine been ordered but one film taken at 4½ years showed collapse of the fourth to the seventh thoracic vertebrae at which point the film was cut off. In addition to the generalized skeletal decalcification there was calcification of the digital blood vessels of the hands and feet (Figs. 2 and 3), almost certainly arterial, although arteriography would have been necessary to prove it. A radiograph of the hands two years previously had shown some osteoporosis around the affected joints but no calcification of the digital vessels. By this time the child had been given a total of 1.47 g. of prednisolone. In spite of the vertebral collapse and severe osteoporosis it was decided

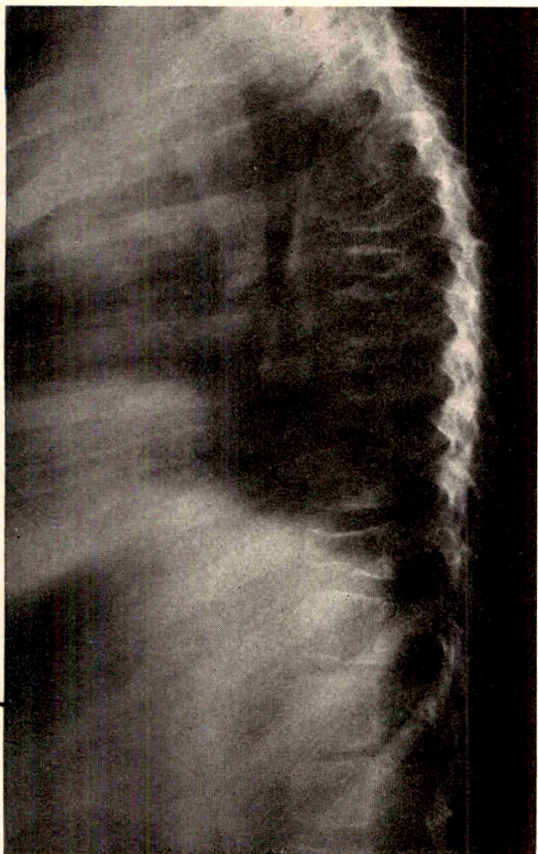


FIG. 1.—Radiograph of spine showing osteoporosis and deformity of vertebrae.

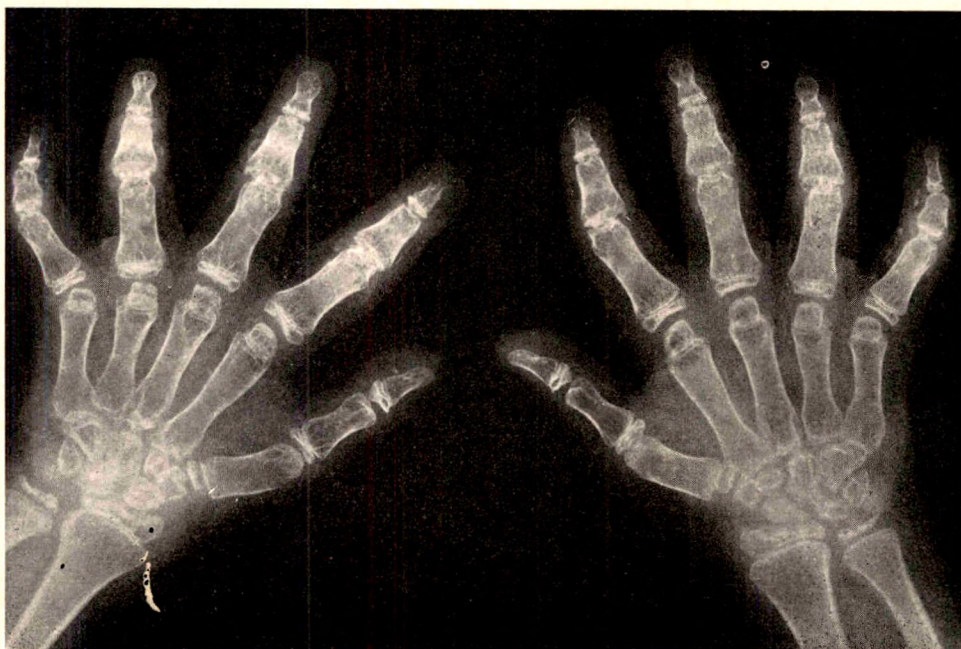


FIG. 2.—Radiograph of hands showing calcification of the digital blood vessels.

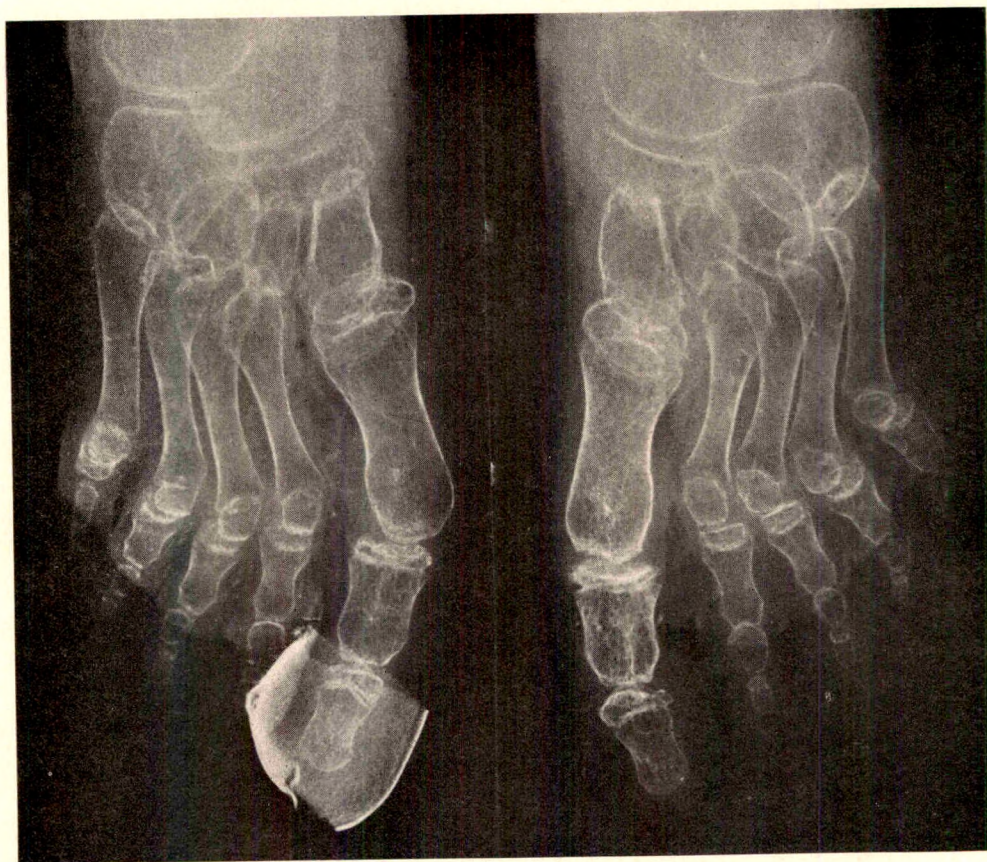


FIG. 3.—Radiograph of feet showing calcification of the digital blood vessels and the first right metatarsal artery.

to continue hormone therapy in view of the striking clinical improvement obtained.

A calcium balance was then undertaken to see whether the use of methylandrostenediol would increase the retention of body calcium (Fischer and Hastrup, 1954). The results are summarized in Table 1 for the balance period of 30 days. The diet which the child had been taking for some time and which contained a large amount of milk was first analysed and then kept con-

stant. She had not been having vitamin D supplements and none were given during the balance. The calcium balance was carried out for 10 days on 10 mg. of prednisolone daily. On the eleventh day methylandrostenediol, 30 mg. daily, was added and the balance was continued for another 20 days. No change in calcium or phosphorus retention due to the methylandrostenediol was noted. The calcium and phosphorus balances were very strongly positive throughout the whole period. The average calcium retention by children of early school age was reported as 26% of the intake by Holmes (1945). This child was retaining 59% of her calcium intake.

The considerable retention of calcium in spite of continued prednisolone therapy was thought to be due to the process of recalcification of the skeleton brought about by increased exercise. The calcium balance had presumably been negative during the protracted period of bed rest. The biochemical findings at the time of the balance are summarized in Table 2. The only abnormality was a rise in globulin to 4.2 g./100 ml. with a normal albumin of 4.2 g./100 ml. Electrophoresis showed an increase in α_2 and γ globulins consistent with some

TABLE 1
RETENTION OF BODY CALCIUM AND PHOSPHORUS

	Average Daily				Percentage Daily Retention
	Intake (mg.)	Output		Retention (mg.)	
		Urine (mg.)	Stool (mg.)		
Calcium	1,140	27	439	674	59
Phosphorus	993	134	316	543	55

activity of the rheumatoid arthritis. The B.S.R. was 18 mm./hour (Westergren) on the same blood sample.

TABLE 2
BIOCHEMICAL FINDINGS

Calcium	= 10.6 mg./100 ml.
Phosphorus	= 3.8 mg./100 ml.
Alkaline phosphatase	= 16 K.A. units/100 ml.
Urea	= 20 mg./100 ml.
Cholesterol	= 180 mg./100 ml.
Bilirubin	= 0.5 mg./100 ml.
Sodium	= 139 mEq./l.
Potassium	= 4.8 mEq./l.
Chloride	= 99 mEq./l.
Albumin	= 4.2 g./100 ml.
Globulin	= 4.2 g./100 ml.
Total	= 8.4 g./100 ml.

After five months' treatment with prednisolone the child was able to wash and feed herself and walk on her own and so she was allowed to go home. At home she has continued to improve gradually on prednisolone therapy, 10 mg. daily for two years and, more recently, on 7.5 mg. daily. She can now walk a quarter of a mile. During this period the amyloidosis has regressed with much diminution in the size of the liver and spleen and a reduction of the albuminuria to 25 mg./100 ml. in the 24-hour collections. As previously given, the Congo red test in January, 1955 showed 95% fixation of dye by the tissues at the end of one hour. In May, 1956 the fixation was 87%, in December, 1956 it was 75%, in March, 1958 it was 56% and in March, 1959 it was 65%. Recent radiographs show that general recalcification of the skeleton has taken place although it is not yet normally calcified. There is in addition a diminution in the calcification of the digital vessels. At no time has the blood flow to the digits appeared deficient. On the contrary, one persistent sign of activity has been the dilatation of capillaries at the base of the nails. The skin has never shown any thickening suggestive of dermatomyositis, however, and there were no lupus erythematosus cells in the blood samples examined.

The blood pressure is now 130/100 mm. Hg, whereas before A.C.T.H. therapy it was 110/80 mm. Hg. While 20 mg. of prednisolone was being given daily it was 150/120 mm. Hg.

The child's growth has been retarded since the onset of her illness. Even during this last year when she has been in better health than in previous years there has been an increment of $\frac{1}{2}$ in. only in height. The height of 43 in. at 9 years is well below the third percentile and the weight of 47 lb. is at the third percentile. Her weight has been kept reasonable by slight dietetic restriction. The bone age, judged by the maturation of the skeleton as a whole, is 13 years, i.e. four years in advance, and menstruation occurred abnormally early at the age of 8 years. Pubic hair is present but no axillary hair has appeared. There is early breast enlargement (Fig. 4).

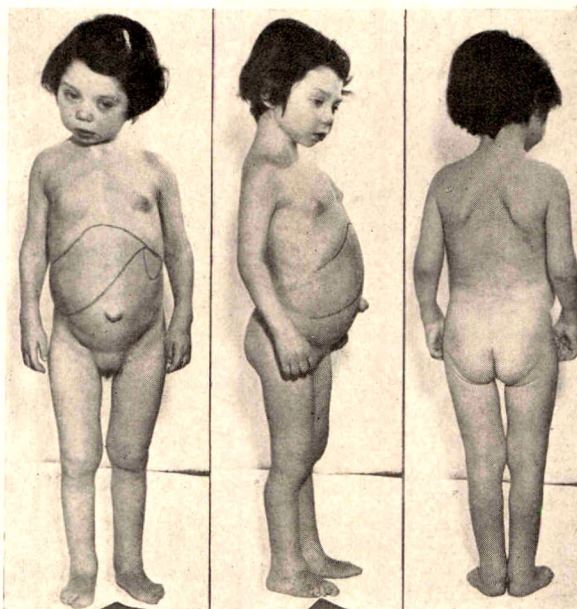


FIG. 4.—Patient aged 9 years.

To summarize, this child has suffered from active rheumatoid arthritis for seven years. During the course of her illness pericarditis has occurred twice. She has developed amyloidosis and gross decalcification of the skeleton with vertebral collapse and calcification of the digital vessels. Prednisolone therapy, even at a late stage, led to a marked improvement in her condition.

Discussion

It is interesting that prednisolone therapy produced so much improvement in this child after four years of severe rheumatoid arthritis, when A.C.T.H. gel, admittedly in relatively smaller dosage, was ineffective in the early stages. The hypertension is probably due to prednisolone but it should be noted that the blood pressure tended to be high even before A.C.T.H. was first given. Early menstruation may also be the result of hormone therapy. Stunting of growth due to the disease would be expected but may have been accentuated by prednisolone. The disparity between the stunting and the advanced bone age is difficult to explain, although the advanced bone age and early menstruation may be related pituitary effects. Amyloidosis is a rare, although recognized, complication of rheumatoid arthritis in childhood. Its regression with improvement in the rheumatoid condition has been described by Parkins and Bywaters (1959).

The vertebral collapse was first noted at the age of $4\frac{1}{2}$ years following one year's treatment with

A.C.T.H. in very moderate dosage. It is unfortunate that radiographs were not taken immediately before prednisolone therapy was begun because in retrospect it is not possible to separate the possible effect of the hormone from that of immobilization in producing generalized decalcification of the skeleton and concomitant calcification of the digital vessels. No other tissues appear to be involved in the process of metastatic calcification. I think that the severe decalcification was chiefly due to prolonged bed-rest with almost complete immobilization of the joints due to rheumatoid arthritis and possibly not at all to A.C.T.H. or prednisolone therapy in view of the small to moderate dosage employed (Welch and Forsyth, 1953; Luder, 1954). This view is substantiated by the finding of a strongly positive calcium balance in the month in which the radiographs were taken and by the gradual recalcification of the skeleton which followed during the next three years of continuous prednisolone therapy. Along with this improvement in skeletal calcification it is of interest to note the diminution in calcification of the digital vessels.

Regarding the aetiology of the calcification of the digital vessels, several possibilities must be considered.

Although amyloidosis affects blood vessels, calcification of the deposits in the vessel walls does not occur.

Calcification of peripheral vessels has been described in a few children with severe chronic renal disease, e.g. hydronephrosis, polycystic kidneys, chronic glomerulo-nephritis, aplastic kidneys or renal tubular disease (Stryker, 1946; Andersen and Schlesinger, 1942; Cochrane and Bowden, 1954). Secondary hyperparathyroidism is ruled out as a cause of metastatic calcification in this patient because of the normal serum calcium and phosphorus levels and the normal blood urea despite amyloidosis of the kidney.

In infants, calcification of the coronary arteries with death from heart failure has been described by several authors (Baggenstoss and Keith, 1941; Andersen and Schlesinger, 1942; Stryker, 1946; Cochrane and Bowden, 1954; Hunt and Leys, 1957). The aetiology of the calcification in these cases was unknown and, although some of the large arteries were involved occasionally in addition to the coronaries, the digital vessels were not affected.

The rare condition of pseudoxanthoma elasticum, if widely disseminated, may be associated with calcification of the vessels due to an infiltration of the degenerated elastic tissue by calcium phosphate. This child, however, did not show the skin discolouration or eye changes associated with this

disease. Neither did she have the skin changes of dermatomyositis which may be associated with subcutaneous deposits of calcium.

Vascular calcification in children has been described in hypervitaminosis D and also in severe forms of idiopathic hypercalcaemia (Schlesinger, Butler and Black, 1956; Rhaney and Mitchell, 1956). In retrospect, idiopathic hypercalcaemia was probably present in a similar case described by Lightwood (1932). In these conditions osteosclerosis occurs. Moreover there is no record of the present child having received extra vitamin D.

It is well known that hormone therapy may lead to osteoporosis and that in Cushing's syndrome renal calculi may form. However, no reference has been found to digital vessel calcification due to hormone therapy.

Acute and subacute forms of arteritis associated with rheumatoid arthritis have been discussed recently in the literature (Levin, Rivo, Scott, Figueroa, Fred and Barrett, 1953; Cruickshank, 1954; Kemper, Baggenstoss and Slocumb, 1957), but no mention has been made of calcification of the affected vessels.

Immobilization by bed-rest and particularly total immobilization in severe joint disease causes marked skeletal decalcification. Hypercalcaemia with renal calculi formation may follow but calcification of vessels has not been noted in the literature from this cause.

One cannot therefore be dogmatic regarding the aetiology of the digital vessel calcification in this child. It seems most likely, however, that prolonged immobilization led to decalcification of the skeleton with liberation of calcium which became deposited in digital vessels possibly damaged by rheumatoid disease.

Summary

A girl crippled by rheumatoid arthritis, complicated by amyloid disease, was found to have calcification of the digital vessels in association with widespread decalcification of the skeleton. After prednisolone therapy she was able to walk again. In the next three years considerable recalcification of the skeleton occurred with some diminution in the calcification of the digital vessels and marked regression in the amyloid disease.

I should like to thank Professor J. L. Henderson for his encouragement to publish this report, and Professor R. W. B. Ellis for access to the Edinburgh records. The calcium balance estimations were made by Dr. T. Bird, then of the Department of Pathology, Queen's College, and the photographs were prepared by Mr. T. King, Queen's College.

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BILATERAL TRIGGER THUMB IN INFANTS

BY

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From Pinelands, The Cape of Good Hope

(RECEIVED FOR PUBLICATION JULY 10, 1959)

'Trigger thumb' or 'snapping thumb' in infants is a curious digital restriction in the very young and perhaps is best referred to as a tendovaginitis stenosans of the sheath of the flexor hallucis longus muscle as it is found in infants. The characteristic feature of this condition is the sudden overcoming of involuntary resistance occurring in the normal range of movement of the interphalangeal joint of the thumb, after which movement is again free. Sometimes the sudden overcoming of the resistance is accompanied by a snap. When the physician first sees the infant the interphalangeal joint of the thumb is usually actively inextensible beyond an angle of about 150°. Frequently flexion from full extension is blocked at a slightly more obtuse angle in the same child but the resistance is more readily overcome voluntarily by the stronger flexor tendon.

The recognition of this entity has been mentioned in one or two American text-books of orthopaedic surgery and it has been written about in the continental European literature but there is scarcely a mention of it in the British medical press other than two case reports of the bilateral condition by Rose (1946) in Australia. For this reason a case of bilateral trigger thumb in an infant of 14 months is submitted. Also, it clearly fixes the manner and time of its clinical appearance.

Case Report

T.S. was just 14 months old when her father, who was fond of playing with his young children, noticed for the first time that her left thumb seemed fixed in flexion ('bent at the knuckle'). He believed that had this persistent digital flexion been present earlier he would have observed it. No other member of the family group, in which there were five adults (including two grandparents), had seen or remarked upon the state of the thumb. The father, therefore, was inclined to believe that the limitation of movement had come on suddenly. At the time of his initial observation he immediately compared the two thumbs but the active and passive ranges of movement of the other thumb were normal as far as he could make out.

When the parent brought the infant for advice it was

noted that the affected thumb's interphalangeal joint could not extend beyond about 135°, to which angle both active and passive movements were painless. Forced passive extension to the maximal normal limit was sudden and painful enough to make the infant cry. Soon after, within five minutes of the forced passive extension, the joint spontaneously resumed its position of persistent restricted extension. Palpable over the flexor pollicis longus tendon and at the head of the first metacarpal was a lentil-sized nodule in the subcutaneous tissue. The diagnosis was straightforward. However, no comparable nodule in the other thumb was noted at the time. An open operation to split the tendon-sheath only was successful and the skin sutures were removed eight days later. At this time comparison again of the two thumbs showed no functional difference; but 10 days after the removal of the sutures, or 18 days after the operation, the observant father saw with interest and some little distress that an identical limitation of extension of the other thumb had taken place.

Review of the Literature

In 1933 Compere collected notices of 40 cases of trigger thumb and established its rarity in infancy. His collection included bilateral cases in adults and these were comparatively frequent. There were only two reports of cases in children. His case of bilateral snapping thumb came to him when she was 20 years old and she was able to recall that she had had the condition without any real disability resulting since the age of 4 years. His other case he saw when the baby was 9 months old but the mother informed him that both thumbs snapped into extension soon after birth.

Compere (1933) quotes Hauck reporting an infant girl with bilateral involvement. So up to the time of Compere's article only three instances of bilateral trigger thumb appear to have been reported, of which two were in the infant age group. Lipscomb (1944) reviewed 190 cases of tendovaginitis stenosans and found among them only 11 of the thumb, none of these unilateral and none in children. In 1936 Jahss made a point of the fact that because of the rarity of trigger thumb in infants he had not had a

case referred to him for treatment that had been correctly diagnosed. Most of the diagnoses made had been 'congenital contracture of the thumb'. He reported nine cases. None of the mothers of his cases could recall exactly how long the condition had been present in her child. Jahss states that he actually saw 15 cases but confirmed only 10 by operation and their ages ranged from $3\frac{1}{2}$ months to 15 years. Three were bilateral and their ages 15, 2 and $1\frac{1}{2}$ years when he saw them. In 1946 Rose in Australia published two more instances of trigger thumb in both hands, the ages of the infants being 9 months and 2 years respectively. Sprecher (1949) in America reported 12 cases, in none of whom was there an audible snap. In four, locking of the thumb had been noticed immediately or soon after birth, and in the others before the age of 3 years. In three of Sprecher's cases both thumbs were affected and in two cases with one thumb showing the limitation the other thumb was functioning normally although a palpable nodule was present in the tendon. Sprecher refers to Beck who reported six cases but no details are given. Zadek (1942) also described two unilateral cases in whom there was symptomless thickening on the tendon of the other thumb. In 1953 White and Jensen discussed a series of nine cases of trigger thumb, whose ages ranged from 15 months to 6 years. Two cases had a family history and five patients came from the same island in the Hawaiian Group. All cases were unilateral. It was in 1953 also that Chiari was able to give the results of his own method of a subcutaneous operative approach to the stenosed part of the tendon sheath in 100 children. Although Chiari admits to the stenosis being found for the first time in later infancy and childhood, he nevertheless rather unhappily uses the term congenital contracture of the thumb (*angeborenen Daumenkontraktur*). There is no doubt from his article that his 100 cases were all stenosing tendovaginitis. His contribution would have had an added value if Chiari had analysed his remarkable series into age groups, sex, time of onset, whether uni- or bilateral and so on. It is to be hoped that he will do so. That Chiari was able from his own practice to collect 100 cases on whom to apply his surgical technique suggests the probability that there were others differently treated and that in his part of the world trigger thumb is not so rare an entity as we are inclined to regard it.

Discussion

I have been able to collect nine undoubted cases of bilateral trigger thumb in infants from my review of the available literature. About 25% of the cases

manifesting trigger thumb in infancy have been bilateral. When one attempts an aetiological hypothesis which excludes trauma, the causative factor for trigger thumb in adults, one inclines to wonder why it is that many more, if not all cases, do not sooner or later become bilateral. Perhaps closer follow-up observation of unilateral trigger thumb is desirable. Despite Chiari's big series which leaves an impression that tendovaginitis stenosans is not uncommon, all available evidence emphasizes the rarity of the bilateral state.

Clinical recognition of the stenosed sheath of the long flexor tendon of the thumb in infants is made by the fact that there is a persistent, painless limitation of extension of the digit to an angle of about 150° . Passive attempts to extend the interphalangeal joint fully are somewhat painful but possible and sudden, when a snap may be heard. Once the joint is fully extended passive flexion is neither painful nor will it produce a snap. Some parents have given a history of a gradual increase of resistance to full extension and the production of the trigger thumb effect, and eventually a complete locking of the joint at a definite angle. The thumb, when first seen in the locked state or when no attempt has been made passively to overcome the resistance to extension, has been confused with a true congenital contracture of the thumb. In this latter disability, however, there is hyperextension of the metacarpophalangeal joint and flexion of the interphalangeal joint, both of which are fixed. Compere mentions rheumatism, neuritis, periostitis, tenosynovitis, tuberculous osteitis, and recurring dislocation at the interphalangeal joint as some of the mistaken diagnoses in his experience.

Whereas trigger thumb in adults is of fairly frequent occurrence and can usually be associated with a story of preceding repeated minor trauma, bilateral trigger thumb in adults is rare and unrelated to infancy. In infants there has been no history forthcoming of any sort of trauma excepting one case of Zadek's in which there had been definite injury to the thumb so that it was treated at first as a traumatic dislocation and only later did an antecedent trigger thumb show up. In my case the onset of the bilateral manifestation could be looked on as a simultaneous happening.

The stronger pull of the flexor tendon keeps the nodule on the proximal side of the stenosis, the primary pathology being in the tendon sheath, and Zadek regards the tendon thickening as a reaction to pressure on the tendon by the stenosing band. In one case he states that the tendon was oedematous. Jahss described a pathological study of the sheath in which there were hyalinized connec-

tive tissue and fibrous villi but there were no adhesions and no free fluid.

Because trigger finger and trigger thumb in adults can almost always be associated with trauma, Compere postulates that in infants there is a predisposing factor and he proposes that it is the acuteness of the angular change of course and pull of the flexor pollicis longus tendon at the metacarpophalangeal joint; but if this were the factor or even a factor it has been stated that the condition would be much more common, certainly in its bilateral form. It has also been postulated that a congenital anomaly of muscle insertion initiates the condition in the foetus which might account for those cases discovered at or soon after birth. The lateral head of the flexor pollicis brevis muscle and the adductor pollicis muscle have been incriminated. Possible additional bands between these two muscles and passing over the tendon sheath of the long flexor, or an abnormally close relationship between these three muscles may be extra factors, but surgical enquiry has not supported these ideas. And yet a variation of the short flexor muscle of the thumb has been described in which a part of the muscle may be inserted separately into the ulnar side of the proximal phalanx of the thumb with the adductor muscle, when it is known as the first volar interosseous muscle. To reach this point of insertion the shorter muscle would have to cross the long flexor tendon of the thumb.

Sprecher sectioned a piece of the involved part of the tendon and reported evidence of trauma indicated by numerous lymphocytes and monocytes in the stroma of the tendinous tissue. So Sprecher believes that the child's tendency to grasp its thumb into its palm produces a sharp kinking of the tendon over its ligamentous attachment to the bone and

that this is enough to provide the necessary trauma. He was also of the opinion that because the newborn infant will grasp its thumb in this way it could hold it in the same way *in utero*.

Whether any ethnic influence plays a role is unknown, but a hint of some such possible factor has been put out by White and Jensen who recorded a family history in two of their cases and five others of Filipino ancestry who came from one island in the South Pacific. Chiari's series was collected in Germany. My case came of allegedly pure Germanic and Sicilian stock.

Summary

An account is given of a curious affection of the sheath of the long flexor tendon of the thumb in infants. Although the incidence of the unilateral condition is by nearly all reports rather uncommon, that of the bilateral state is a rarity. It goes colloquially by the names of 'trigger thumb' or 'snapping thumb' but is perhaps better described terminologically as tendovaginitis stenosans. A report of a case is followed by a review of the literature and a discussion of possible aetiological factors in its development.

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PAROXYSMAL TACHYCARDIA IN A CHILD SHOWING STOKES-ADAM AND WOLFF-PARKINSON-WHITE SYNDROMES

BY

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From the Lady Ridgeway Hospital for Children, Colombo, Ceylon

(RECEIVED FOR PUBLICATION JULY 13, 1959)

Paroxysmal tachycardia in infancy may be accompanied, as in the adult, by some disturbance giving rise to pallor, restlessness, dyspnoea, weakness and usually cardiac insufficiency and decompensation. A labile autonomic nervous system makes infants particularly vulnerable to paroxysmal forms of tachycardia. Exactly what it is that starts this disorder or rhythm is frequently obscure and consequently functional autonomic disturbances must often be assumed to be responsible.

The Stokes-Adam syndrome seen in adults in the course of the development of complete heart block is not often seen in children and the case described below, occurring in a child of 2 years during an attack of supra-ventricular paroxysmal tachycardia, is of unusual interest. The symptoms of cardiac insufficiency, more commonly seen in such cases, were conspicuous by their absence in this instance.

Case Report

A boy (P), aged 2 years and 3 months, was admitted to the Lady Ridgeway Hospital for Children, Colombo, at 9 a.m. on January 14 with a history of 10 to 15 'fits' a day. He had had two fits in the out-patients' department while awaiting admission, each fit lasting one to two minutes. The previous history was that the child was healthy after a normal delivery. There was no illness of any importance before these fits. He had had similar fits when 8 months old for four days, each fit lasting about a minute, and there were four to five fits each day. A similar attack of fits occurred three months later when the child was admitted to this hospital for a few days. He was discharged and had been admitted again subsequently to this hospital and to a branch hospital at Ragama. Each time he was discharged after a few days with a diagnosis of fits due to round worms and, on one occasion, epilepsy. The mother stated that the fits were not associated with any fever. The child became semi-conscious for a few seconds before the fit, and appeared to be quite normal afterwards.

On examination at about 9.30 a.m. the child appeared to be a healthy well-fed boy weighing 22 lb. (9.98 kg.).

There were slight pulsations over the veins in the neck. The heart was within normal limits and there were no murmurs. The rate was very rapid—about 220 per minute—and the pulse was regular and very small in volume and tension. There was no cyanosis nor dyspnoea and the child was seated on the bed.

The skin turgor was normal and the fontanelles were closed. There was no spasticity of the limbs or neck. The cranial nerves were normal. The abdomen was soft and there were no masses palpable. The liver and spleen were not palpable. While this examination was going on the child quite suddenly became very pale and fell back on the bed in a faint. He remained so for about 30 seconds. He next had a convulsive fit involving both limbs, lasting about one and a half minutes, and soon regained consciousness; he then appeared to be quite normal in colour and behaviour. It was noticed that during the faint there were missed beats and the heart rate was very slow, about 60 to 64 per minute. The child sat up in bed a few minutes later and seemed to be quite normal and unconcerned with what had happened a few minutes earlier. The heart rate was now very rapid and rose to 140 and later 200 per minute. An electrocardiogram was taken soon after and proved very interesting, as the child had a similar faint and fit while this record was being taken. In fact the record was interrupted during the fit for a minute or so. The recording proved an interesting study. Fig. 1 shows a paroxysmal tachycardia of the supra-ventricular type at a very rapid rate of 260-270 per minute. There are short periods of complete cardiac-standstill varying from 0.6 to 0.8 sec. It was noticed that the child fainted off during this period of asystole and when he recovered a few moments later the rhythm was slow and irregular at first but later was quite regular and rapid and soon reached a rate of 240 per minute. While the E.C.G. was being examined the child had a similar faint and fit and appeared to be quite normal soon after the fit. He was treated with a sedative syrup of chloral (gr. 3 in 1 drachm) 6-hourly and Tab. Digoxin 0.25 mg. 4-hourly from 10 a.m. The pulse rate continued to be over 200 for 24 hours, but 12 hours later it slowed down as shown in the table.

The child continued to have fainting attacks and short

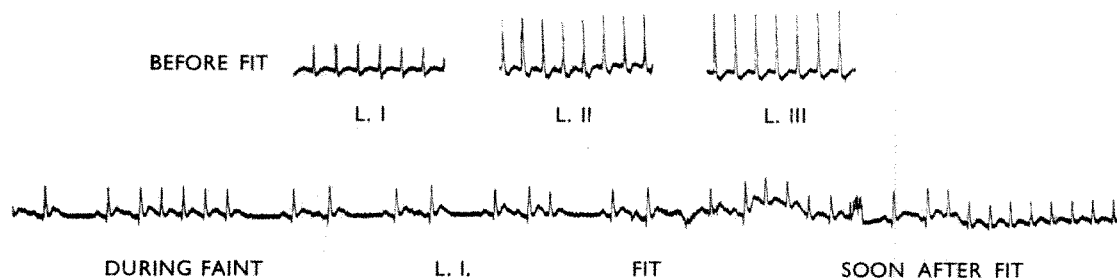


FIG. 1.—Paroxysmal tachycardia of supra-ventricular type.

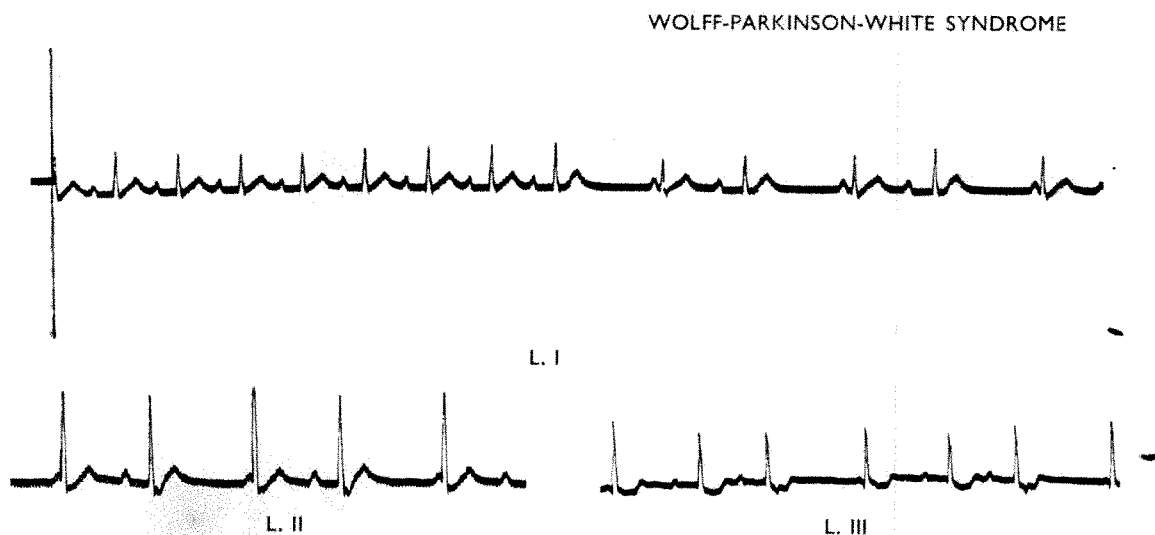


FIG. 2.—E.C.G. taken after discontinuing Digoxin.

fits about three or four times during this period but was generally comfortable and playing in bed.

On January 17, after discontinuing the Digoxin, another electrocardiogram was taken (Fig. 2). It is seen that Lead 1 starts off with eight normal beats but the ninth is absent while the PR interval of the tenth beat is 0.08 sec. This part of the record shows that every

second or third beat has a short PR interval and that each of these beats is preceded by a dropped beat. The shortened PR interval varies from 0.02-0.08 sec. (the normal in infants being not less than 0.12 sec.). The QRS complex is widened 0.11 sec. with slurring of the upstroke of the R wave (the normal in infancy being 0.05 to 0.06 sec.). There are therefore on this record complexes of the Wolff-Parkinson-White syndrome type, each being preceded by a dropped beat. The slurring and widening of the QRS complex with short P waves indicates the presence of the Wolff-Parkinson-White syndrome without any doubt. The E.C.G. records on January 23 (Fig. 3) and February 17 (Fig. 4) showed a

TABLE			
		Treatment	Pulse Rate/min.
January 14	10 a.m. ..	0.25 mg. Digoxin	240
	4 p.m. ..	"	240
	7 p.m. ..	"	240
January 15	11 p.m. ..	"	240
	3 a.m. ..	"	230
	10 a.m. ..	"	220
January 16	2 p.m. ..	"	220
	6 p.m. ..	"	210
	10 p.m. ..	"	120
January 17	6 a.m. ..	"	160
	10 a.m. ..	"	140
	2 p.m. ..	"	136
January 17	6 p.m. ..	"	108
	10 p.m. ..	"	112
	6 a.m. ..	"	120

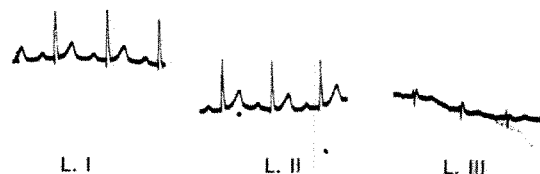


FIG. 3.—E.C.G. showing normal picture with normal rhythm one week later.

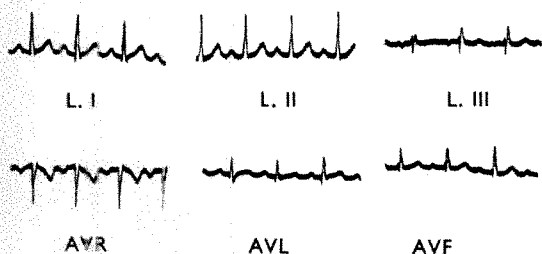


FIG. 4.—E.C.G. showing normal picture with normal rhythm one month later.

normal picture with normal rhythm. On January 26 the child had two short fainting attacks without any convulsions and Digoxin was given again for four days. The child had another faint on February 2 and on February 17, after being quite well and happy, he left us. A follow-up two years later showed the child to be in good health, with a heart normal in rhythm and rate.

Comment

The case recorded is that of a 2-year-old child who had a paroxysmal tachycardia of the supra-

ventricular type and showed fainting attacks followed by fits very similar to the Stokes-Adam syndrome seen in adults with heart block. A further interesting feature was that on recovering the child showed the presence of the Wolff-Parkinson-White syndrome in the electrocardiogram. This latter syndrome is an electrocardiographic entity and has been the subject of much discussion and study since it was originally described by Wolff, Parkinson and White (1930). Gleckler and Lay (1952) have described the Wolff-Parkinson-White syndrome in a 4-month-old infant with paroxysmal tachycardia in whom an electrocardiogram made on cessation of the arrhythmia showed the presence of the syndrome. The interest in this case is that, besides the Wolff-Parkinson-White syndrome, this child also showed the presence of Stokes-Adam while in hospital.

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SPONTANEOUS HAEMORRHAGE FROM THE INTERNAL CAROTID ARTERY IN A CHILD

BY

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(RECEIVED FOR PUBLICATION JULY 27, 1959)

The case described below shows a child in whom there was a spontaneous haemorrhage from the internal carotid artery in relation to a para-pharyngeal abscess.

Case Report

A boy aged 7 was admitted to hospital after having vomited a small quantity of blood on two occasions during the preceding day without warning or preceding nausea. For six days he had been ill with a sore throat, lassitude and malaise, while the left side of his face and neck had developed a swelling which suggested a diagnosis of mumps.

The boy was pale and inert. He showed a mild pyrexia (100.2° F.) while his pulse was 120 per minute and blood pressure 120/80. A red swelling was visible in the left wall of the pharynx but its extent was not defined as trismus limited inspection. The lymph nodes along the left jugular vein were enlarged.

Three hours after admission a copious haemorrhage occurred. An observer related that the child neither coughed nor vomited but that the blood seemed to well up from the throat.

An immediate operation was deemed necessary and performed by Mr. R. S. Lewis. Under anaesthesia the swelling in the left of the pharynx was confirmed and found to extend from the level of the soft palate down to the epiglottis. The overlying mucous membrane was not discoloured by ecchymosis or inflammation. It bore a ragged opening below and behind the left tonsil leading into a cavity containing blood clot.

An incision was made along the anterior border of the left sternomastoid muscle; the soft tissues were indurated and stiffened while the exposure of the left external carotid artery was impeded by enlarged lymph nodes. The short length of external carotid artery exposed allowed ligation below the origin of the superior thyroid artery.

During the ensuing night a small haemorrhage occurred, but for the next 36 hours the child improved and there was no bleeding until suddenly two days after operation this boy, without warning, lost two or three pints of blood in a cascade from his mouth in three minutes, quickly becoming unconscious, pale and pulseless.

A blood transfusion was started and the child was taken to theatre where the wound was re-opened and the left common carotid artery was divided between ligatures. Three pints of blood were transfused.

Next morning the boy was sitting up in bed cutting paper flags although examination showed signs of a mild right hemiplegia with slight weakness in the right limbs, an accentuated right ankle jerk and extensor plantar response.

During the next 12 hours the child slowly lost consciousness and remained in coma for 48 hours. To preserve the cerebral circulation from spasm and thrombosis Priscol and heparin were given and both stellate ganglia were injected with Xylocain (1.5 ml. of a 2% solution).

Recovery of his mental state was gradual. For the next five days he was half conscious and when discharged two weeks later he was fully conscious but showed an emotional lability and lack of concentration. The only neurological sign was slight right facial weakness.

Later reports of his schooling show that, although showing imagination, he was backward at first through lack of reasoning power, but that he has now caught up with his fellows.

Discussion

The severity of the haemorrhages, especially the last, showed that a major artery was involved. That bleeding recurred after ligation of the external carotid artery and was controlled by ligation and division of the common carotid artery showed that the bleeding vessel was the internal carotid artery. The section of the common carotid artery removed the sympathetic supply to the distal part, preventing spasm and minimizing ischaemic changes in the brain (Rogers, 1947). Although knowledge of the site of bleeding would have suggested the common carotid artery for ligation in the first instance, it is doubtful if this alone would have arrested the haemorrhage in view of the free collateral circulation through the branches of the external carotid artery.

This case is notable in having by the two ligatures

effected complete arrest of blood flow into the left internal carotid artery with little, if any, permanent change in the brain. In the recorded cases (Wood, 1953) 30% of such cases ended fatally or showed brain damage.

Finally this case stresses the nearness of the internal carotid artery to the pharynx. It may lie as little as 2 mm. below the mucous membrane.

Recent literature shows few cases in which a carotid artery was ligated for spontaneous rupture of the internal carotid artery; one was described by Woodruff in 1945 and one by Beck in 1947.

On the other hand, Salinger in 1934 described

over 200 cases of abscess in relation to the pharynx, of which 13 required ligation of one carotid artery.

We thank Mr. R. S. Lewis and Dr. Mary Wilmers for permission to publish this case.

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BLOOD URIC ACID LEVELS IN MOTHERS AND INFANTS AT BIRTH

BY

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This study has been undertaken to determine a pattern of blood uric acid levels in normal mothers and their full-term infants at the time of birth. Blood samples were taken from the umbilical vein to determine the infant levels and from the maternal venous blood at the time of delivery to estimate the mothers' blood uric acid levels. The uric acid estimations were done by the method of Folin and Trimble (1924). Table 1 summarizes the findings of this study.

Steenstrup (1956) has discussed hypo-uricaemia occurring during pregnancy and, in an extensive study of plasma uric acid levels in 280 cases, he found a moderate hypo-uricaemia to be present during the greater part of normal pregnancy. He used the method of Praetorius and Poulsen (1953) for estimating his uric acid levels. Crawford (1939) found a rise in plasma uric acid levels during labour and a fall in the early puerperium so that normal values were reached by the third day after

delivery. The height of the rise during labour appeared to depend on the length of labour. Benedict's (1922) colorimetric method was used for these estimations.

In the present study the maternal ages of the 21 cases ranged from 18 to 41 years and their parity included seven primigravidae, nine with one previous pregnancy and the remainder having had from two to 10 previous infants. The 21 infants included eight males and 13 females. The blood uric acid levels in the mothers ranged from 6.9 mg./100 ml. to 2.6 mg./100 ml. and in the infants from 7.3 mg./100 ml. to 2.4 mg./100 ml. In 12 cases the mother's level was higher than that of her infant.

This study shows the rather wide range of blood uric acid levels existing in the cord blood of normal male and female newborn infants and in their healthy mothers' blood taken at the time of delivery; there does not appear to be any correlation between these uric acid levels. In three cases the mother's

TABLE 1
BLOOD URIC ACID LEVELS IN NORMAL MOTHERS AND THEIR FULL-TERM INFANTS AT BIRTH

No.	Maternal Age (yr.)	Parity	Birth Wt. (lb. oz.)	Sex	Blood Uric Acid Level	
					Mother (mg./100 ml.)	Infant (mg./100 ml.)
1	20	Primipara	8.3	M	6.5	5.0
2	20	Primipara	7.9	F	3.6	5.5
3	22	Para 1	7.10	M	4.1	3.9
4	23	Para 1	7.8½	M	4.6	3.4
5	25	Primipara	5.4½	M	2.6	2.4
6	32	Para 1	7.12	M	4.6	4.0
7	33	Para 1	6.15½	M	4.2	5.8
8	18	Primipara	8.8½	M	3.8	3.1
9	23	Primipara	6.4	M	4.9	2.8
10	32	Para 3	7.8½	F	3.9	3.5
11	21	Para 1	7.0½	F	4.7	4.2
12	34	Para 4	7.11½	F	6.7	4.3
13	22	Primipara	7.8	F	3.0	3.8
14	41	Para 10	6.10½	F	6.9	6.5
15	29	Para 1	6.12½	F	3.6	3.8
16	27	Para 1	8.2	F	4.4	4.5
17	22	Para 2	6.10½	F	5.1	7.3
18	37	Para 7	6.6	F	2.6	5.3
19	21	Para 1	5.8½	F	3.9	3.7
20	21	Primipara	7.15½	F	4.0	4.5
21	29	Para 1	8.2½	F	4.0	5.0

level was over 6 mg./100 ml. and in two infants cord blood levels were also above this figure; only in one case was the level above 6 mg./100 ml. in both the mother and her female infant.

The authors wish to thank Professor E. H. Cluver for allowing them the facilities to undertake this investigation; they are also grateful to Professor O. S. Heyns, Dr. F. Daubenton and Dr. L. G. R. van Dongen for allowing them access to their patients, and to the labour ward nursing staff of the Queen Victoria Maternity

Hospital for facilitating the collection of blood specimens.

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BOOK REVIEWS

Paediatric Neurosurgery. Ed. IRA C. JACKSON and RAYMOND K. THOMPSON. (Pp. xvi+564. £6 5s.) Oxford: Blackwell Scientific Publications.

There are two ways of writing a textbook on a small specialized branch of medicine. The first is to describe the practice of one particular school, its great virtue being that it sets a standard against which others can measure their own work. Ingraham and Matson have already successfully exploited this technique in their *Neurosurgery of Infancy and Childhood*. The second method is to assemble a team of contributors each of whom speaks of his own subject. Ideally this should lead to increased erudition and brilliance; in practice it tends to sacrifice unity of presentation.

The first few chapters of this book are devoted to a detailed account of various clinical methods. The section on lumbar and ventricular puncture is very full but, rather irritatingly, subdural puncture is dealt with partly here and partly in a later section. There is an interesting account of the use of electromyography; the section on the E.E.G. is so short and so general that it would have been best omitted. The section on anaesthesia lists many possible methods, but gives little practical advice. An interesting innovation is the introduction of a chapter on medical conditions resembling surgical problems, but it is strange to find no mention of Devic's disease here, although the papilloedema seen in this condition may lead to the suspicion of intracranial tumour.

Congenital malformations are dealt with at some length. The advice on the management of spina bifida cystica is clear and sensible but the indications for operation on spina bifida occulta are muddled and the writer has apparently abandoned any effort to classify his results. In the section dealing with encephalocele, there is the barest mention of hydrocephalus, and none of ultimate mental retardation, though both complications are not infrequent.

In the section on inflammatory diseases the term débridement (of wounds) is used as a synonym for excision, which it is not, and the advice that persistent post-infective subdural effusions should be drained into the pleural cavity is controversial, to say the least. It is also a pity that although the writers of other sections devote much space to the technique of well-known surgical procedures, antero-lateral decompression for the relief of paraplegia in spinal tuberculosis is barely mentioned.

The author of the section on vascular malformations of the nervous system sets out a series of case histories separated by relatively brief general remarks. The result is that although given much useful information,

a reader not already familiar with the subject is left in doubt which of the clinical observations are of general importance, and which apply only to the case described.

The section on intracranial tumours is long and not wholly satisfactory. Most of the references are old (before 1950) and it is unhelpful to refer simply to 'Bailey' when the bibliography lists two different Baileys with eight references between them. I cannot understand the statement that 'medulloblastomas occur almost exclusively in males and the same is true of craniopharyngiomas' (p. 225). In any event it is inconsistent with the further statements that there is no specific sex predilection in craniopharyngiomas (p. 268) and that medulloblastomas are three times more frequent in males than in females (p. 314). The author's views on the prognosis in medulloblastomas are unduly gloomy and take no account of the work of Ralston Paterson and his colleagues.

The section on peripheral nerve tumours, in which is included neuroblastoma, is sketchy and would have been better omitted.

The sections on trauma to the head and spine are both practical, though it is wrong to use 'hypothermia' as a synonym for control of pyrexia and curious that although 3rd and 6th cranial nerve palsies are mentioned, nothing is said about damage to the 4th cranial nerve, which is as common as any post-traumatic oculomotor disturbance. From time to time the contributors, and even the editors themselves, seem to lose sight of the fact that they are writing about infants and children. There is an editorial note in the section on spinal injuries which refers to intervertebral disc herniations as due to a degenerative process: this is surely not the case in children.

There are separate chapters on the surgery of involuntary movements and leucotomy (lobotomy). The wisdom of this is doubtful. The application of the former to paediatrics is not properly worked out, and many would think that the latter should never be practised at all in children. There is also a chapter on the surgery of epilepsy but it is devoted entirely to advice on local resection of the cortex, and the author starts from the proposition that no surgery should be done for epilepsy below the age of 12. The surgery of infantile hemiplegia, particularly hemispherectomy, is nowhere mentioned.

There is much useful material in this book, but it seems to fall between two stools. The paediatrician will find more surgical detail than he needs, while the trained neurosurgeon will find some chapters insufficiently authoritative. In a second edition there should be ruthless pruning, and the standard of the bibliographies at the end of each chapter should be raised.

Lehrbuch der Chirurgie und Orthopaedie des Kindesalters.

Ed. A. OBERNIEDERMAYR. (3 vols. Pp. 375, 1087, 266; illustrated DM. 620.) Berlin: Springer Verlag. 1959.

This is by far the largest textbook on paediatric surgery written since the war. It consists of three volumes and more than 1,500 pages, but in spite of its size the book is not as complete as one would expect and some of the chapters are surprisingly small. The largest part of the work of a paediatric surgeon is undoubtedly abdominal surgery and it is, therefore, surprising that only 150 pages are devoted to this subject. The quality of the different chapters varies considerably. Those written by the editor and his paediatric surgical colleagues include accounts of most of the recent advances in this field and describe the personal experience of the writers. The same cannot be said of some of the other chapters written by 'General' and 'Specialist' surgeons. The section on plastic surgery by H. Gelbke is excellent and deserves special praise, but it is obvious that some of the authors have not had much experience with children and are inadequately informed of recent advances in paediatric surgery.

Professor Oberniedermayr has performed a gigantic task in editing this monumental textbook, which will be of value to surgeons and paediatricians alike. It is unfortunate that the high price of the book will prevent most people acquiring it.

Growth Diagnosis. By LEONA M. BAYER and NANCY BAYLEY. (Pp. 241. 80s.) Chicago: University Press. 1960.

The importance of assessing a child's growth progress and developmental status is now widely recognized amongst paediatricians not only in relation to endocrinopathies, chromosomal aberrations and mental retardation, but also in obese children, and children with education problems, operated cardiac conditions, poliomyelitis, spasticity and many other complaints. There exists no succinct guide, however, telling the busy clinician in relatively few words and charts just how to do this. The present book is a praiseworthy, though by no means entirely successful, effort to provide one. It is exceedingly well produced and less excessive in price than most books coming from the United States at present.

The first 68 pages are devoted to descriptions of methods for studying growth in the individual patient, and the next 144 to describing in detail the application of these methods to 22 children, of whom eight are healthy children, followed from birth to maturity in the Berkeley Longitudinal Growth Study, and 14 are children with gigantism, various sorts of dwarfism, pseudohermaphroditism, hypothyroidism, precocious puberty, obesity, castration and hypogonadism. The book is clearly not meant to tell the reader anything much about how a child grows, and has no discussion on growth and the influences of genetics, environment, secular trend and so forth; it is presumed, I imagine, that the reader will be acquainted with one of the texts on growth, or with the excellent chapters devoted to it in Nelson or Holt and MacIntosh.

The measurements advocated are height, weight, sitting height (greatly preferable to the use of span in

both authors' and reviewer's opinion), biacromial and bi-iliac diameters. The authors fail to mention the clinically indispensable measurement of subcutaneous fat with calipers, and give illustrations of a quite outdated instrument for measuring the two diameters. A technique of taking front, side and rear view body photographs is given, though the rear view pose adopted by the subject in their illustration has little to recommend it, and the opinion that 'box cameras are preferable' has a quaint Victorian ring. The Greulich-Pyle and Pyle-Hoerr atlases for bone maturity at wrist and knee are recommended and briefly introduced. An anthropometric chart is used in which the five measurements given above are plotted in terms of standard deviations away from the mean. This is incorrect for weight, since the skew in its distribution makes the standard deviations *not* correspond to the usual percentiles; in any case, percentile charts are easier to understand for all measurements. The tables used as the basis for mean values and standard deviations date from 1931 (the Gray-Ayres data) which, considering the great secular trend over the last fifty years, is surprising. Scales for rating secondary sex character appearance are given, but in boys no distinction is made between ratings for pubic hair and genitalia, though the two do not always exactly keep step with each other. There is a long section describing the authors' own excellent work on androgyny of build, and another giving Dr. Bayley's very useful tables for prediction of adult height from height and skeletal development during childhood. There are also, and interestingly, new standard charts of height and weight for age, from birth to maturity, in which a most praiseworthy effort is made at including information on the developmental as well as the chronological age of the child. Lines are given for the physically accelerated and retarded child as well as for the average; the difficulty would seem to be that one cannot distinguish on them a pathologically small child from a pathologically retarded one, as one can by plotting height on a conventional chart in terms first of chronological, then of skeletal, age.

The clinical material is of great interest, illustrated with excellent photographs, and followed for the most part over long periods of time. Despite the criticisms above, there is no question that these descriptions constitute the best published accounts to date, from the growth point of view, of cases with clinical growth disorders. This is indeed what anyone familiar with the authors' work and particularly with Dr. Bayley's many and deeply thought out papers on physical and mental growth would expect. It is the more pity that a rather critical review is unavoidable. A curious insularity seems to have settled over the Bay when the book was written; astonishingly, only four references appear to papers published outside America; one of these refers to Fröhlich's original paper of 1901; the other three to standard texts of over twenty-five years ago, all of which have been reissued since in later editions. The authors are certainly to be congratulated on essaying a very necessary task; the result, despite blemishes, which will doubtless be removed in the second edition, is well worth the attention of paediatricians.

Weight Gains, Serum Protein Levels, and Health of Breast Fed and Artificially Fed Infants—Full Term and Premature. By B. LEVIN, HELEN M. M. MACKAY, CATHERINE A. NEILL, V. G. OBERHOLZER and T. P. WHITEHEAD. (16s.) Medical Research Council, Special Report Series No. 296. 1959.

This is a valuable report which should help to set standards and remove a lot of uncertainty. The clinical material was composed of over seven hundred babies, over two-thirds full term and under one-third premature, almost all born at the Mothers' Hospital in North-East London. The mean weights of the full-term infants are similar to those of published standards for 'normal' infants, but the smoothed curves now presented are a valuable addition to the somewhat scanty British data on this subject. The curves for premature babies confirm the view that if weights are grouped by age from conception, then after 40 weeks the curve is similar to that for full-term infants. As regards feeding it is generally concluded that full-term babies in this series, fed either on breast milk or on dried cows' milk, had similar weights, similar protein levels, a similar incidence of infections and, with iron medication, similar haemoglobin levels. For premature babies, however, it is concluded that human milk is an inadequate food in early life, due to the low protein content. Biochemical investigations established standards of normal for total serum protein, albumin and globulin in the first eighteen months of life in full-term infants. The serum protein levels of premature infants were much lower than for full-term infants but changes for age were similar in both. After eight days of age the serum protein level was not influenced by the type of food given. Valuable data on the serum protein components and especially on serum gamma globulin levels in the cord blood are also included. The whole report represents a great amount of co-ordinated labour and must be regarded as a standard work of reference.

A Symposium on Immunization in Childhood. (Pp. 139. 17s. 6d.) Edinburgh: Livingstone. 1960.

After protracted discussion the symposium adopted two schedules for immunizing children. The first was, 5 weeks to 6 months—three injections of pertussis vaccine; 7-10 months—two injections of poliovaccine; 10-12 months—two of diphtheria and tetanus and a fourth of pertussis; 15-18 months—a third injection of diphtheria and tetanus and of poliovaccine. Booster doses of diphtheria and tetanus at school entry and 8-9 years. The second schedule was, 2-6 months—three injections of a triple vaccine of diphtheria, tetanus and pertussis; 7-10 months—two injections of polio; 15-18 months—a fourth injection of the triple vaccine and a third of polio; booster doses of diphtheria and tetanus as for schedule 1. In each schedule smallpox vaccination was to be carried out some time during the first 5 years, with re-vaccination at 8-9 years, and B.C.G. was to be given between 10 and 15 years. Schedule 1 entails 11 visits and 13 injections, while schedule 2 needs nine visits and 10 injections.

Both these are formidable programmes, demanding much of the public health authorities and not a little of the mothers and children, not to mention the fathers. The fact that two schedules had to be promulgated shows how opinion can be divided, and the pros and cons of each in relation to the different disease vaccines are fully and freely discussed in the text. All through there is evidence of the desire to confer optimum protection with the minimum of backsliding on the part of the patient, and this is clearly why the two different schedules are propounded.

This publication is most timely and will help to some extent to delimit the problems concerned with vaccination programmes even if the tentative answers to them are somewhat equivocal. And as with so much recent writing, one is left with the feeling of what an unpleasant person in the woodpile is type 1 polio virus.

1959-60 Year Book of Pediatrics. Ed. SYDNEY S. GELLIS. (Pp. 493. 60s.) Published by Year Book Publishers, Chicago, and distributed by Interscience Publishers, London.

Dipping into this year book is just like going to an international paediatric congress in the United States. It does not matter which particular section one attends, there is the same series of well-chosen papers, generally of the proper length but some overrunning their time, some passing without comment but others attracting discussion. Naturally the majority of the papers are by Americans, and all the commentators are American also.

The congress has various things, such as personal contacts and 'cokes', which the book lacks; but these apart, I believe one could profit as much by reading the book as by attending the congress—and it is a lot cheaper.

Actualités Pédiatriques, 1ère série. Ed. MARCEL LELONG. (Pp. 323; 63 figs. Fr. fr. 3,900.) Paris: G. Doin et Cie. 1959.

From the Hospital of Saint-Vincent de Paul comes a series of 19 chapters by different authors dealing with one or other of the growing points of paediatrics. Each article is complete in itself and, while not exhaustively reviewing its subject, is a reasonably full account of recent work. The volume is sponsored by Professor Marcel Lelong who himself contributes a chapter on hiatus hernia. These articles give one a rapid appraisal of a particular subject but would not be a jumping-off ground for further research as they do not assess the literature to any degree.

Sewage Contamination of Bathing Beaches in England and Wales. (Pp. 24. 2s. 6d.) Medical Research Council Memorandum No. 37. London: H.M.S.O. 1959.

Readers of this pamphlet will be relieved to learn that the danger of contracting infectious illness from bathing where sewage is discharged into the sea is negligible.



SPINAL DYSRAPHISM

AN ORTHOPAEDIC SYNDROME IN CHILDREN ACCOMPANYING OCCULT FORMS

BY

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Much interest has been shown in the pathology of the more gross developmental anomalies of the spinal cord and its coverings and in their clinical manifestations, most of which are not amenable to treatment. It has not been appreciated that lesser anomalies can also produce disabilities, that they can be diagnosed in life and that they can frequently be treated by surgery before the secondary effects have become severe and irreversible. Clinical experience over a number of years of the many children sent to orthopaedic clinics with various types of foot or lower limb defect led us to suspect the presence in some children of a spinal cord lesion responsible for a particular pattern of lower limb abnormalities. Such children were watched carefully and the development of their abnormalities and subsequent radiological and neurological investigations confirmed us in our belief that in a number of those children presenting at first with relatively trivial foot defects, there was an underlying spinal anomaly causing their troubles which might well be dealt with at an early stage, thus preventing further disability and perhaps improving such disability as had already occurred. We therefore decided to operate, at first upon those children whose abnormalities were beginning to increase seriously, and later, in the light of experience gained, upon all those in whom we had good reason to suspect the presence of a spinal lesion.

We now believe that we can identify with certainty a syndrome associated with and diagnostic of spinal dysraphism when there is an occult lesion affecting the spinal cord. By diagnosing this condition early we can undertake spinal surgery before severe deformity and disability of the lower limbs has occurred confident that surgery will be beneficial. The clinical manifestations are for the most part orthopaedic in that it is the lower limbs and feet

which usually suffer. The treatment in the first place is principally in the field of neurosurgery since the removal of the primary cause, when it is possible, demands laminectomy and exploration around the spinal cord within the dura mater. Subsequent orthopaedic care will be needed only to correct established deformity if the diagnosis has been made late.

Spinal dysraphism is a term which has been applied to failure of complete development in the midline of the dorsal aspect of the embryo. The extent of this failure may be of mild, moderate or severe degree. The best known clinical form is meningocele which is an example of an overt lesion, but the lesion may not be visible on the surface nor make itself evident clinically. Spina bifida occulta is such a condition and is so commonly noted in routine x-ray investigations that it is regarded as a curiosity rather than as an entity with possible clinical implications. Ingraham and Lowrey (1943) have given an indication of the types of lesion to be found clinically, and other writers have described the particular lesions which interested them. None appears to have regarded these lesions as being of the same origin except Lichtenstein (1940), who revived the term spinal dysraphism and under this heading grouped disorders according to whether they manifested themselves as arising from cutaneous, mesodermal or neural derivatives of the dorsal median region of the developing embryo.

In this communication we are concerned only with those forms of spinal dysraphism which directly or indirectly affect the spinal cord and spinal nerves and our aims are to describe these lesions, to indicate the general pattern of the associated orthopaedic syndrome and to draw attention to the value of spinal surgery as a preventive measure when undertaken early.

The Lesions

Lesions affecting the spinal cord or cauda equina may be classified into three groups, those which produce a traction effect, those which exert local pressure and those which combine traction and pressure.

The Traction Group. In the growing child, there is a difference between the rate of growth of the spinal cord and that of the vertebral column. This is described as the ascent of the spinal cord within the vertebral canal, because the length of the latter, as the vertebral column grows, increases at a greater rate than the length of the spinal cord. At birth the distal end of the spinal cord is normally situated at or about the upper border of the body of LV.3 and at the end of growth, in adult life, is situated at the lower border of the body of LV.1 or the upper border of LV.2 (Streeter, 1919). Any lesion which prevents this ascent of the spinal cord will do so by fixing it at a definite level in the vertebral canal. In such circumstances the spinal cord or nerve roots or both will be stretched as the bone column grows and this stretching will produce injury either to the tracts within the spinal cord, or to the nerve fibres and indirectly to both of these by interfering with their blood supply. In all probability the commonest lesion of this type is diastematomyelia in which the spinal cord is bifid in part of its course. This is also the most easily diagnosed lesion when it is associated with a bone septum lying anteroposteriorly across the vertebral canal and transfixing the spinal cord. This bone septum can be seen on a plain x-ray film. A septum is, however, not always calcified; it may be fibrous and therefore not demonstrable by plain x rays.

Fibrous bands are also found tethering the spinal cord or cauda equina to the bone or skin directly or through attachment to the meninges. These may be associated with the fibrolipomata found in the pressure type of lesion. A tight filum terminale has often been cited as a similar traction lesion.

The Pressure Group. The best known type is the intrathecal lipoma, which consists of a fatty fibrous mass lying inside the dura mater. In some cases the fatty fibrous mass is entirely extradural; in others it may be extradural and intrathecal. Another type of pressure lesion occurs when a fibrous band constricts the lower end of the spinal cord situated at an abnormally low level (Léri, 1926). Occasionally, when the vertebral canal is already narrowed by inversion of one or more laminae, pressure may arise from increasing thickness of the bone with normal growth.

Within this group may also be placed those cases

of congenital scoliosis resulting from hemivertebrae which develop paraplegia at about the age of 12 years.

The Combined Group. This group consists of a variety of lesions which incorporate external pressure by a fatty fibrous mass or by a transverse band with traction by some form of fibrous band attaching to the meninges, bone or skin.

Symptoms and Signs—Early Stages

Occult forms of spinal dysraphism are rarely evident at birth. At that time, the function of the spinal cord may not be impaired, but as the child grows, a dysraphic lesion will begin to have an effect, either by preventing the spinal cord from 'ascending' within the vertebral canal or by pressure from the increasing size of some abnormal tissue such as a lipoma. The effect, then, of a dysraphic lesion is a gradual interference with conduction in the spinal cord or its nerve roots, so that according to the site of the lesion there will be a gradual loss of sensation and a slowly developing weakness of some muscles leading to muscle imbalance and ultimately to deformity.

Symptoms. A child of any age is commonly referred because of a peculiarity of gait or because of distortion of one shoe, itself the result of a peculiarity of gait unnoticed by the parents. Sometimes a child attends because of poor posture associated with a short leg or because one leg has been noticed to be shorter and thinner than the other.

Pain is not a feature but there is occasionally a complaint of pain in one or more metatarsophalangeal joints which may be associated with a protective kind of gait. This is possibly the earliest evidence of this syndrome since in such cases at this stage there is no foot deformity.

Gait. The abnormality of gait, almost imperceptible early on, consists in an elevation of the first metatarsal head as though something like a drawing pin were underneath it, the great toe usually remaining flexed. Occasionally this is accompanied by adduction movement of the fore foot, but there is no evidence of abnormal function in the foot or toes when standing or when not bearing weight; voluntary actions are normal. In the course of review the peculiar action is more easily seen and the deformity which follows is quite obviously the result of this peculiar action; even so the foot may still have a normal appearance at rest. If allowed to continue, the pes cavo-varus observed only when walking becomes fixed. The arc

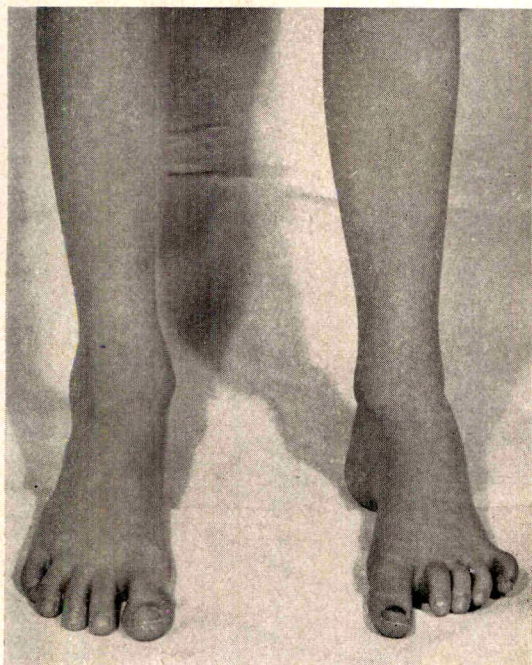


FIG. 1a

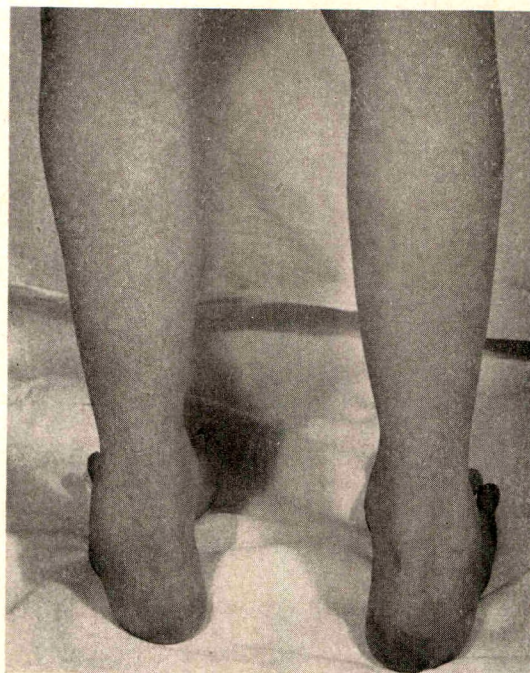


FIG. 1b

becomes higher, the forefoot more adducted and more inverted, and the toes become clawed. The result (Fig. 1 a, b and c) is not unlike the deformity seen in some cases of poliomyelitis and cases of relapsed club foot.

Lower Limbs. Examination of the lower limbs almost always reveals a shortening of one leg and foot, although it may be absent or very slight in the early stages. The affected leg is smaller in girth, both in the thigh and in the calf. The shortening of the leg rarely progresses to a final discrepancy of as much as 2 in. and it is usually much less, but the shortening of the foot becomes exaggerated by the cavo-varus and clawing of the toes. Peripheral circulatory deficiency is sometimes evident, showing as a lividity or cyanosis.

In fully developed cases the combination of muscular imbalance and ischaemia produces fixed clawing with atrophy of the toes.

Nervous System. Reflexes are usually normal but may progress to an extensor plantar response and exaggerated, and later, absent knee and ankle jerks, as may occur in all progressive neurological lesions. Sensory changes have not been detected in younger children owing to their unreliable testimony, although some have exhibited trophic

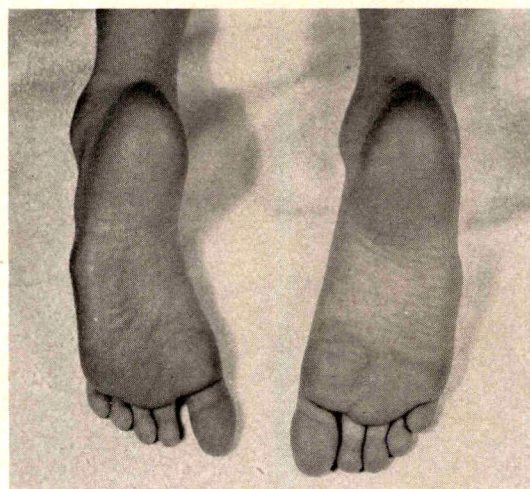


FIG. 1c

FIG. 1.—Case 6. The deformity of the left foot in a moderately severe case. Right foot normal.

- a Showing the inversion of the forefoot and the degree of cavus. Early clawing of the toes. Standing, bearing weight.
- b Showing the inversion of the heel. The thinning of the calf is not well shown. Standing, bearing weight.
- c Showing the shape of the sole and the shortening of the foot. Kneeling; the feet are not touching the background.

changes. Older children manifest the usual alterations in sensation in the leg through dulling of light touch and hypersensitivity on deep pressure to total loss of sensation and also the characteristic saddle shaped area of analgesia over the buttocks and posterior surface of the thighs. We have not tested for loss of anal tone which other authors have found to occur (Jones and Love, 1956). Testing sensation in any child is difficult because the child will often give the answer which he thinks the examiner wants. The results are therefore commonly unreliable.

Back. There is frequently no superficial evidence of abnormality in the spinal column; occasionally a bifid spinous process may be palpable. The visible abnormalities in the back are cutaneous or subcutaneous; they are not present in every case and when present are not always associated with neurological deficit or foot deformity although these may develop later. They consist of the following:

(1) *Subcutaneous lipoma.* This is often associated with spina bifida occulta and exists as a diffuse soft mass of fat, usually over the sacrum.

(2) *Abnormal hair in the lumbo-sacral region.* Coarse hair several inches in length may be found which is maximal in the midline and exists from the time of birth. On occasion a silky down limited to a discrete area is found.

(3) *Angioma.* A superficial angioma may be found in or near the midline in the lumbo-sacral region.

(4) *Dermal dimples.* Skin depressions near to the midline with fixation of the epithelium to underlying layers may indicate the presence of a spina bifida.

(5) *Dermal sinuses.* Dermal sinuses near the midline may mark the outlet of a continuous fibrous or fistulous tract extending directly into the spinal cord but the cutaneous opening may be minute and may not be seen without a very close inspection of the back. These sinuses must not be confused with the common pilonidal sinus which has no connexion with the subarachnoid space and which is situated in the midline.

Progression and Later Stages

The majority of our cases have presented in the manner described or with the foot deformity already established. In the latter cases the mode of development of the deformity is no longer evident; there is already a pes cavo-varus with mobile clawing of the toes and except that weight is borne on the outer border of the foot no muscle can be seen to be overacting. The leg and foot are short and the arch of the apparently unaffected foot is sometimes a little high but within normal limits. When the

foot deformity is established, the reflexes become abnormal and there may be sensory changes. With continued progression, sensation becomes increasingly impaired, trophic ulceration occurs and the deficient circulation becomes more obvious.

Another method of presentation is that of Case 2 (see Table) where the appearances of the lower limbs were similar to those seen in cases of myelocoele. We have not otherwise seen calcaneo-valgus deformity developing after birth, but it is likely to occur probably where the spinal cord is affected at a high level and these cases are more likely to develop paraplegia. Other authors have mentioned such cases with paraplegia or weakness of the lower limbs and an unsteady gait.

A history of incontinence is unusual in early cases but bowel and bladder symptoms may develop later. There may be incontinence which cannot be diagnosed in a young child only just old enough to be expected to learn control (Case 2). Urinary incontinence of the type associated with a neurological bladder which empties itself only when fully distended is difficult to identify. Double incontinence with loss of bladder and bowel sensation may supervene in time.

In this description of the progression of lower limb abnormality it is clear that the syndrome is very similar to that occurring with spinal tumours except that the rate of progress in the latter is very much faster so that foot deformities have not time to develop. Paraplegia is likely to be the end result in both types of untreated case, although rare following spinal cord lesions associated with spinal dysraphism. The foot deformity which develops gradually over a long period in the dysraphism cases precedes the paraplegia.

Our experience of adult cases is limited and it appears that they are not often diagnosed. Their deformity has presumably been static for a number of years and they are unlikely to come for orthopaedic attention except for supply of surgical footwear. Those who develop trophic ulceration may be recognized if the clinician is aware of the syndrome, otherwise they are most likely to come to notice if they develop urinary or bowel dysfunction (Case X). Our personal adult cases were recognized by reason of attendance for supply of footwear, one of them having trophic ulceration.

Radiological Investigations

Apart from clinical examination and periodic review, the other chief investigation required is radiology. Every child (in the absence of a myelocoele) who shows a peculiarity of gait, poor posture associated with a short leg, a short and thinner leg,

progressive deformity of a foot, absent deep tendon reflexes or evidence of sensory impairment in the lower extremities, should have careful radiographic examination of the spine. Lichtenstein (1940) has pointed out that bone anomalies may be absent but it is our experience that plain films usually show congenital anomalies of the vertebral column such as spina bifida, which is the commonest abnormality, or hemivertebrae. A bone septum (diastematomyelia) may be shown. Spina bifida of even the slightest degree is almost always present in this syndrome but the bone abnormality is not necessarily at the site of the lesion, which may be situated some distance away as in Case 2.

Myelography is valuable for more exact diagnosis and for localization of the lesion but it should not be done lightly; its purpose is confirmatory. It will demonstrate space occupying lesions and obstruction to the flow of the opaque medium and if there is sufficiently clear definition of the filum terminale and nerve roots a myelogram may indicate the site of the conus medullaris. Occasionally the spinal cord may be seen to be held against the neural arches instead of being in its normal position lying against the vertebral bodies. Some traction lesions, however, are not demonstrated by myelography. Whilst screening it is necessary to examine the patient supine as well as in the classical positions. We have used myodil as the opaque medium; at lumbar puncture for its injection, cerebrospinal fluid is removed for examination and is usually found to be normal.

Diagnosis

At present the early case is not easy to diagnose confidently and usually the progress of deterioration has to be watched over a long period before the diagnosis can be established. There is a wide differential diagnosis and any history elicited from the parents must be considered with caution. A previous diagnosis of poliomyelitis may be suspect since it may have been applied *post hoc* to explain abnormality. A story of old injury likewise must not be accepted without further enquiry.

In the first place, the diagnosis depends upon the presenting symptoms. The peculiar gait suggests many conditions, a plantar wart, early hallux rigidus, injury to sesamoids underlying the first metatarsal head, foot strain, or too small a shoe. Pain, if present, may bring to mind March fracture, early hallux rigidus, trauma, foot strain, osteochondritis of a metatarsal head or of the navicular, or lumbar nerve root irritation.

The cases of short foot and leg of the variety for which no cause is found are distinguishable from

those due to spinal dysraphism in the course of long term review by the foot shape, function and the gait, which continue to be normal. Other possible causes of a short foot and leg are old bone infection, previous fracture, poliomyelitis and hemihypertrophy or angiomatosis of the other limb.

Disease of the nervous system must be excluded, e.g. neurofibromatosis, tumour of the cauda equina, Friedreich's ataxia, the distal (Gower's) type of myopathy, peroneal muscular atrophy, polyneuritis and cerebral palsy.

In the late case, the limb deformity and the neurological deficit make the diagnosis straightforward.

Treatment and Results

Excluding cases of diastematomyelia with a bone septum evident on a plain x-ray film that ought to be operated on at once, the only treatment possible in the early stages is a passive correction of the shortening by the use of raising on the shoe, with or without irons. This treatment is rarely effective for any length of time. When the presence of a neurological deficit has been established, laminectomy should be performed after myelography. Surgical exploration of the vertebral canal, including opening the dura to permit inspection of the spinal cord, is intended to remove the cause of the disability by releasing the anchoring of the spinal cord or by excising the cause of pressure. The results expected are not that the lower limbs will return to normal, nor that previous incontinence will be cured, although these things may happen if the case is dealt with early enough, but that there will be no further deterioration nor increase in the lower limb abnormalities and deformities. The changes which have taken place in the spinal cord and nerve roots may be irreversible so that recovery cannot occur. The operation is essentially preventive. Orthopaedic treatment will be necessary to correct the established foot deformity and residual muscle weakness. After removal of the primary cause of muscle imbalance, full use can be made of normal function and growth in the correction of any postural foot deformity. Without removal of the primary cause, orthopaedic treatment may temporarily correct a postural deformity but is ineffectual except as a short term expedient.

Illustrative Cases

In the Table we present a summary of our first 16 fully investigated cases. There are many other cases under review some of which are awaiting myelography. The cases in the summary are given in order of myelography and some, which are not cases of the syndrome described, have been in-

Case	Sex	Date of Birth	Date First Seen	Syndrome	Neurology†			Sens
					K.J.	A.J.	Plantars	
1	F	18.12.46	17.12.56	Poor circulation lower limbs; right foot slightly smaller than left	++ +	+ +	? F	
2	M	19.5.53	12.1.55	Dragging inverted left foot and everted right foot; progressive paralysis of lower limbs	+ -	- -	E E	Abn
3	F	5.3.45	7.9.55	Left pes cavus with clawing and dropping of forefoot; left leg short $\frac{1}{2}$ in.; right foot normal	+ +	+ +	F -	Norm
4	F	8.8.45	12.2.57	Inverting left foot only when walking, distortion of shoe, progressive cavo-varus; right foot normal; legs equal length	± ±	- -	F F	Norm
5	F	11.11.46	23.7.47	Originally clawed outer toes left and severe valgus both feet; not seen 1951-55 and then left foot smaller than right; progress: left cavo-varus and clawing; poor skin circulation; sacral naevus and excess hair	+ +	+ -	F -	
6	M	21.12.46	9.6.55	Left cavo-varus; left foot shorter than right; left leg $\frac{1}{2}$ in. short; sacral hairy patch	+ +	+ +	F E	Norm
7	F	30.8.50	1.11.54	Right foot smaller than left since birth; developed mild cavo-varus; sacral hair	- +	- +	E F	Norm
8	M	21.8.52	4.11.57	Short left leg and foot; pes cavus R. and L. worse with progressive increase of varus in left; increasing weakness of left foot; falling over frequently	+ +	+++ +	? E	
9	F	18.11.47	17.2.58	Mild pes cavus at birth; developed pain left foot with increasing cavo varus and hypersensitivity and impairment of joint sense; left foot smaller than right; legs equal length; weakness dorsiflexors left foot	+ ++	+ ++	F F	Abn
10	F	30.8.45	14.11.51	Left club foot treated at birth; short right foot and leg developed and increasing cavo-varus of both feet, later left leg was shorter	- -	- -	- -	Trophic loss of : in both
11	M	2.2.56	9.2.56	Bilateral club feet with full correction obtained by age of 4 mths; persistent overaction of Tib. Ant. with progressive increase in cavo-varus deformity starting at age of 18 mths; lower limbs becoming a little spastic	+++ +	+++ +	E E	
12	M	17.4.50	7.9.50	Left leg and foot smaller than right from birth; left foot originally very valgoid but aet. 5 yrs started developing cavo-varus; sacral hair	+ -	+ -	F ?	Abn
13*	F	26.6.46	1.11.54	Since infancy small right foot; sacral fat pad; developed right claw toes and cavus with increasing cavo-varus; left foot mild cavus	- +	- +	- -	Abn
14	M	13.10.54	13.5.58	Persistent inversion left foot; left foot and leg short; pes cavus developing in left foot	+ +	+ -	F E	
15	F	11.12.46	8.3.55	Rapidly increasing left pes cavo-varus; short left foot; legs equal length	+ +	+ -	F E	
16	F	5.7.48	15.7.58	Short right foot and leg, with early right pes cavus; patch of hair over lower thoracic and lumbar region	- +	- +	? F	Abn

* Case referred to us by Mr. J. K. Stanger and Dr. Christine Cooper.

† Neurology: + = present - =

OF SPINAL DYSRAPHISM

Survey Radiograph		Myelography	Comment
septum LV.2; spina bifida LV.3-SV.1	30.3.57	Diastematomyelia	<i>Laminectomy</i> (4.4.57) Bone septum at LV.2/3 level excised; diastematomyelia 1-9 cm.; conus at lower border LV.4
himal spina bifida LV.4 and 5 and SV.1; rearing interpedicular widening at LV.1 indicating enlarging tumour	6.11.57	Total block preventing flow to LV.1	<i>Laminectomy</i> (11.11.57) Transverse pressure band from pedicle to pedicle at LV.1; spinal cord was markedly enlarged at and below this level, probably the result of gliosis
bone abnormality	12.11.57	No abnormality demonstrated	Deformity not progressing after tendon transplants in foot; right foot normal
multiple anomalies of whole spine; tomoph: narrowing of vertebral canal anteriorly by laminae at LV.5	12.12.57	Filling defect left side of LV.5 level	Parents refused operation; left foot deformity slowly developing
lacked spina bifida LV.2—sacrum	31.1.58	Enlarged filum terminale and abnormally caudal conus	<i>Laminectomy</i> (31.3.58) Traction band at LV.3 extra and intra-dural attaching to filum terminale and left S.1 nerve root and holding spinal cord posteriorly; conus at caudal border of LV.3
na bifida LV.5-S.1 with anomalies of vertebral bodies	25.4.48	No abnormality demonstrated	<i>Laminectomy</i> (9.6.58) Traction band, extradural, at LV.5; absence of extradural fat in this area and adherence of ligamentum subflavum to dura; conus at caudal border of LV.3
la bifida LV.4 and S.1 (only four lumbar vertebrae)	30.4.48	Diastematomyelia; conus abnormally caudal	<i>Laminectomy</i> (16.6.58) Fibrocartilaginous septum LV.4; ligamentum subflavum adherent to dura in this area with absence of extradural fat; diastematomyelia limited to area of septum
ior spina bifida at LV.5 and greater degree LV.1	14.5.58	No abnormality demonstrated; some extrathecal myodil	Undiagnosed
derate spina bifida SV.1	23.6.58	No abnormality demonstrated	Physical signs improving; undiagnosed
rked spina bifida TV.9—sacrum	16.7.58	Diastematomyelia; conus situated abnormally caudal	<i>Laminectomy</i> (22.9.58) Bone septum LV.2; conus not seen, but situated below mid LV.4
d spina bifida LV.5 and more severe at LV.1	3.9.58	No definite abnormality demonstrated but theca lay away from the vertebral bodies	Probably cerebral palsy but undiagnosed; not club foot relapsing in the usual manner
nsive spina bifida of whole lumbar spine sacrum	19.9.58	No definite abnormality demonstrated	Under review; foot deformity worse; awaiting laminectomy
la bifida and gross anomalies mid and lower lumbar, with some lower lumbar atrophy	6.10.58	Diastematomyelia (minute); conus abnormally caudal	<i>Laminectomy</i> (9.10.58) LV.3 level, intradural band holding spinal cord posteriorly and rotating it; the spinal cord was bifid immediately cranial and caudal to the attachment of the traction band; the conus lay distal to the level of LV.3 caudal margin
la bifida of LV.5 with caudal extension right lamina of LV.4	12.11.58	Appearances not understood; conus situated abnormally caudal	<i>Laminectomy</i> (24.11.58) Traction band LV.5 lamina to dura and transverse pressure band at LV.4-5 level; conus tip at lower margin of body of LV.4
ked spina bifida LV.3 to SV.1	3.12.58	No abnormality demonstrated; conus abnormally caudal	<i>Laminectomy</i> (25.5.59) Transverse pressure bands at LV.5; absence of extradural fat in this area; conus not seen, probably at caudal border of LV.3
* spina bifida lower thoracic, upper lumbar and ? LV.5; conus at about LV.3 level; graph: bone septum at TV.9	28.1.59	Diastematomyelia	<i>Laminectomy</i> (2.2.59) Diastematomyelia extending about 7 cm.; the cords were adherent to the bone septum

diminished ++ = exaggerated.

Plantar responses: E = Extensor F = Flexor ? = Equivocal — = Absent.

cluded because we thought at the time that the lower limb abnormalities might possibly be ascribed to a lesion of the spinal cord and also because they demonstrate some of the difficulties of differential diagnosis. No fully investigated cases have been excluded.

All of the 10 cases submitted to laminectomy have had demonstrable lesions at operation although the mechanism by which the lesion produced its effect is not clear in every case. In none of these cases has there been any further deterioration and most have improved in an encouraging way. Myelography demonstrated diastematomyelia in six cases and a total block to flow of myodil in one. In the three other cases myelography showed no abnormality in one and in the other two the termination of the spinal cord could be seen to be abnormally caudal.

Four cases are described below in detail, three from our personal series, of which Case 5 had a traction lesion, Case 2 a pressure lesion and Case 14 a combined traction and pressure lesion. Case X (an adult) is given as an example of spinal dysraphism presenting with urinary symptoms resulting from a pressure lesion. This patient was not one of our personal series. He was seen in consultation before operation and is reported here with permission of Mr. Keith Yeates, Dr. John Walton and Mr. John Hankinson.

Case 1 of the series has been reported and discussed elsewhere (James and Lassman, 1958).

Case 5. Female, aged 11 years. This child was first seen at an orthopaedic clinic in March, 1947, when she was 4 months old because the left foot was smaller than the right and the fourth and fifth toes were flexed. The deformity of the toes was treated by strapping and manipulations. In September, 1950, the toes were operated on to correct the deformity. She was not seen between June, 1951 and December, 1955, when she came under our care because she was distorting her footwear. Her left foot was much shorter than the right and there was a tendency to inversion and equinus with dropping of the forefoot. She had a sore on the back of the tendo-achilles and an unpleasant callous under the fifth metatarsal. By July, 1957, the foot condition had altered; the right foot was normal, the left foot was very short, rather high arched with hyperextension activity of the great toe. The muscles of the ankle, foot and toes were functioning, but in voluntary use the invertors overacted. There was still a callous under the fifth metatarsal head. The skin of the left calf was cyanotic and became purple in cold weather and the circulation in the foot was poor. The left leg was at least $\frac{1}{2}$ in. shorter than the right. The left ankle jerk was absent. A pigmented patch to the left side of the sacrum and excessive hair in the lumbo-sacral region were found on examination.

Radiographs of the lumbar and sacral spine demonstrated a marked spina bifida in the lumbar region from LV.2 downwards and also in the upper sacral region (Fig. 2).

Myelogram outlined a midline structure in the terminal theca which was wider in diameter than one would expect for the filum terminale (Fig. 3). This was thought to be possibly anchoring the cord as the conus medullaris lay at an abnormally low level. With this evidence and the clinical history and findings, spinal exploration was considered to be justified.

At operation when the laminae had been superficially exposed, a fatty fibrous mass was found between the laminae of LV.4. This mass was isolated by laminectomy of LV.3 and could be easily lifted off the dura to which it was attached by a fibrous band. The band, accompanied by an artery, passed from the deep surface of the fatty fibrous tissue to the dura, continuing from the deep surface of the dura to the very large filum terminale and to the left first sacral nerve root within the dura. It was approximately $\frac{1}{2}$ in. in diameter and $1\frac{1}{2}$ in. in length and was holding the cord towards the neural arch and away from the vertebral bodies (a state not evident in the myelogram). The spinal cord fell to normal position when the band was divided, but was not seen to shift cranially with the release of tension. The conus lay at the level of the caudal border of LV.3.

The post-operative course was uneventful.

When seen 10 months after operation, the circulation in the left leg was normal and the blue and purple discolouration of the calf no longer occurred. The reflexes

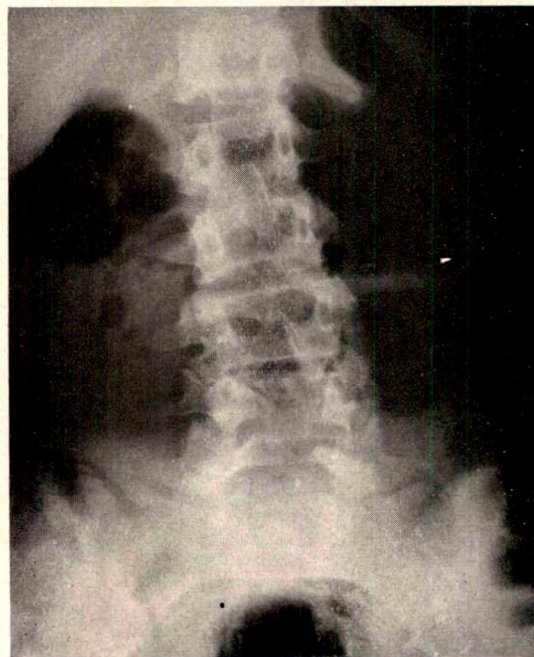


FIG. 2.—Case 5.—Antero-posterior survey view of the lumbo-sacral spine showing marked spina bifida in the lumbar region from LV.2 downwards and also in the upper sacral region.



FIG. 3.—Case 5. Myelography demonstrates in the terminal theca a midline structure which is wider in diameter than would be expected for the filum terminale. The appearances suggest that the spinal cord is anchored down and that the conus medullaris lies at an abnormally low level.

were unchanged. The shortening of the left leg was a little more than 1 in. There was subjective sensory improvement in the foot, in that she could feel, when she put her foot to the ground, a sensory deficit of which she had been unaware before operation. There was increased muscle power and the foot was used in a plantigrade manner, no longer being inverted when walking.

Case 2. Male, aged 4 years. This boy was referred to an orthopaedic clinic in January, 1955, at the age of 20 months because he was not walking on his own. He was healthy and was a full-term baby without neonatal complications. On examination, when he attempted to walk holding on to the furniture, he inverted his left foot and everted his right. When in a standing position, the left foot showed a voluntary tendency to adduction and inversion of the forefoot which the mother had first noticed two months previously. Until then, she had thought that the boy's feet were quite normal. He was not obviously spastic in the left lower limb, but his gait suggested this possibility. He was given irons to wear and slowly gained in strength to be able to walk on his own. Sensation in the legs seemed deficient at about 2 years of age; his lower limbs at this time resembled those of a child with a myelocoele.

He was in hospital for 10 weeks from February to April, 1956, owing to trophic ulceration of the right third, fourth and fifth toes possibly induced by a hot water bottle. During this period, whilst the toes

healed very slowly the deformities of his feet became more severe and more fixed in spite of splintage. By April, 1957, his lower limb power was deteriorating rapidly and he was hardly able to walk barefoot. On October 31, 1957, he was admitted to hospital for investigation, by which time he was unable to walk without assistance even with short irons and boots. He had very little voluntary power of the knees and feet but quite good power of hip movement. It was difficult to determine his degree of sensory loss but he had analgesia to pin prick on the back of the thighs and in the sacral region. The left knee jerk and both ankle jerks were absent and the right knee jerk was just present; both plantar responses were extensor. He had always been doubly incontinent, having no idea when his bladder or rectum were full.

Radiograph of the dorsal, lumbar and sacral spine showed spina bifida of LV.4, LV.5 and upper sacral region with widening of the interpedicular distances with flattening of the pedicles most marked at the level of LV.1 but extending from TV.11 to LV.2 in a lesser degree. The lateral view showed that the posterior aspects of the bodies of these vertebrae were concave. The flattening of the pedicles suggested to the radiologist that the lesion was an expanding one, but he did not think it excluded congenital origin.

Myelography was performed and the myodil flowed upwards as far as the level of the body of LV.1 where a complete block to the upward flow was demonstrated. The radiologist was unable to detect any negative shadow of the spinal cord but several half shadows were present in the myodil suggesting either a gross anomaly or a gross displacement of the cord, probably the former. The myodil passed laterally on both sides into the exit foramen between LV.1 and LV.2 in a manner which suggested a congenital anomaly. The upper border of the myodil in the head down position showed no typical shape but rather an irregular contour in the lateral view.

At operation on November 11, 1957, the spinal cord from TV.12 level caudally to just proximal to the conus was enlarged and white in colour; an extradural fibrocartilaginous band compressed it transversely at the level of the pedicles of LV.1. The cord pulsated cranial to this band and at the conus but not in between, and the band was clearly restricting the flow of cerebrospinal fluid from above downwards. After removal of the band the cord beneath began to pulsate and there was a clear flow of the cerebrospinal fluid downwards. The enlargement of the spinal cord appeared to be due to a congenital abnormality and was not in any way cystic. Microscopy revealed the band to be composed of dense acellular fibrous tissue structurally resembling a ligament.

After operation the boy developed a cerebrospinal fluid fistula and continued to drain cerebrospinal fluid in very large quantities despite further attempts to close the gap. Ventricular drainage became necessary to allow the back to heal and the quantity of fluid discharged through the drain, together with the difficulty of controlling the flow from the fistula, suggested some abnormality of cerebrospinal fluid production. There was no other evidence, internal or external, to suggest

that there was an associated Arnold-Chiari malformation.

After discharge from hospital on January 30, 1958, the strength of his lower limbs developed quite rapidly to begin with but he could not walk without assistance for nine months after operation. Subsequently he began to walk without sticks, wearing a caliper on the right leg. Fourteen months after operation the foot deformities were unchanged; he still lacked voluntary power in the evertors of the left foot and in the invertors of the right, but there has been some recovery in the right calf muscles. Lower limb sensation was difficult to assess but five months after operation his right plantar response was flexor and 12 months after operation a flexor response was obtained on the left side.

His mother stated that approximately one month after discharge from hospital, the boy, for the first time, began to know when his bowels were going to work and after this time he rarely dirtied himself, provided he was near home. As regards micturition, she thought the boy had some feeling but since he wore either a urinal or a napkin he made no effort to control himself.

Case 14. Male, aged 4 years. He was referred to an orthopaedic clinic at the age of 3 years 6 months, because he had been walking with his left foot inverted since the age of 18 months. This tendency was evident in the clinic but there was no real abnormality of the foot apart from slight shortening as compared with the right foot. Examination showed a slight (less than $\frac{1}{2}$ in.) shortening of the left leg; normal right leg reflexes, an absent left ankle jerk and a left extensor plantar response. The left lower limb felt spastic on passive movement.

During the next five months the left foot rapidly developed cavo-varus. The back appeared normal. There was no evidence of bladder or bowel disturbance and the reflexes were unaltered. Sensation was not tested.

Radiographs showed spina bifida of LV.5 and the laminae of LV.4 extending caudally made a curious apparently curved bony ridge crossing the spinal canal at the level of LV.4/5. The interpedicular distance at the lumbo-sacral level was increased (Fig. 4).

Myelography showed no definite abnormality, but suggested that the conus medullaris lay almost at the level of the lumbo-sacral articulation. There were some linear translucencies which could not be satisfactorily explained.

Exploration was decided upon, in view of the neurological deficit in the left lower limb, the rapid development of cavus in the left foot, and the curious myelographic appearances.

At operation the spinous process of LV.4 was found to be expanded on the right side and the right lamina of LV.4 was continuous with that of LV.5. At the level of the pedicles of LV.4 an extradural transverse band firmly adherent to the dura was constricting the spinal cord. Immediately caudal to this transverse band and partly attached to its caudal edge was a cylindrical band 1.0 cm. long with five webbed digital prolongations, which were firmly fixed at their anterior ends to the dura and at their posterior ends to the deep surface of the fatty fibrous tissue which filled the gap. This



FIG. 4.—Case 14. Antero-posterior survey view of the lumbo-sacral spine. The laminae of LV.4 extending caudally exhibit a curious apparently curved bony ridge crossing the spinal canal at LV.4/LV.5 level.

traction band ran obliquely from the midline of the dura in a caudal direction towards the right side in such a way that the whole spinal cord was probably held posteriorly to the right. The traction band was excised, and the transverse band was divided when the dura was opened to expose an apparently normal spinal cord with the conus lying caudal to the transverse band at the level approximately of the intervertebral disc between LV.4 and LV.5. The dura was closed without difficulty but for two or three days post-operatively there was a fluid fistula which healed without further interference. Microscopy of the traction band showed very dense fibrous tissue.

Three months after operation there was no change in the physical signs. At six months, the reflexes were unaltered and there had been no change in the degree of cavo-varus as compared with the state before operation; progression had ceased.

Case X. Male, aged 26. Up to the age of 11 years he had suffered incontinence of faeces and when aged 18 years a small swelling had been removed from over the coccyx. He had begun to experience increasing difficulty in passing urine for two years before his admission to hospital for investigation. Whilst in hospital and shortly after a myelogram, he developed acute retention of urine.

Examination showed sensory loss around the anus and perineal region and on the buttocks in the distribution of the fourth sacral and first coccygeal segments;

there was no abnormality in the lower limbs. Survey radiographs revealed spina bifida of the lower sacral segments S3-S5 which was remarkably wide at S4 and S5.

At myelography, the myodil flowed downwards to the level of the S3/S4 segments. In the supine position the myodil column divided into two lateral columns at the level of the lower border of S5, leaving an oval shaped defect in the outline of the myodil. In the lower lumbar and upper sacral region the appearance of the myodil column suggested that the spinal cord was extending to a very low level.

At operation Mr. Hankinson found a lipoma attached to the skin in the region of the sacral bone defect. The lipoma passed through into the vertebral canal and was continuous with the dural sac and within the dura it was firmly attached to the spinal cord. The spinal cord was of normal thickness and extended to the lowermost portion of the sacrum; the spinal nerve roots passed horizontally to escape through their respective intervertebral foramina in the manner usually seen only in the early stages of human foetal development. The attachment of the lipoma at the periphery of the bone defect was freed and the dura left open and covered with gelfoam. Spontaneous micturition slowly returned and two weeks after operation catheterization was no longer required. The difficulty with micturition has continued to decrease.

Discussion

The picture of this syndrome and its causative lesions which we have endeavoured to draw is based on information from the literature and on a personal series of 16 cases completely investigated and submitted to myelography and more than 20 clinical cases under review and as yet unproven. All these are children. The unproven cases do not include the many cases seen which for no known cause have one leg shorter than the other and a small foot, a combination which is remarkably common in children's orthopaedic practice. Many cases produce a foot deformity which does not progress and, not having developed a neurological deficit, do not appear to justify full investigation and laminectomy. Some of these cases no doubt would have a lesion demonstrable on myelography and surgical correction of the lesion would prevent the full development of deformity but since myelography is dependent on the introduction of a foreign substance into the subarachnoid space it is not an investigation to be carried out without considerable forethought and good reason. Indeed, our policy has been to undertake myelography only if we expect to proceed to operation when the myodil will escape. We have used myodil in our cases and it has been the material used as a routine by the Department of Neuro-radiology for a number of years. So far there has been no complication occurring from its use

and as we gain further experience with myelography we may be able to change our criteria and use it more frequently. The technique of myelography and the understanding of the radiograph appearances need expert management and we are most grateful to our colleague, Dr. Gordon Gryspeerdt, for his skill in this technique and his guidance in interpretation.

It is becoming apparent from our operated cases that some of the traction lesions may give little or no evidence of their presence by myelography. Case 5, reported above, is an example. The myodil column must be examined throughout the whole theca from the cervical region down to the sacrum; Shorey (1955) has reported a case with lesions at two levels, thoracic and lumbar.

If a myelogram fails to demonstrate a lesion which is in fact present, it fails also to provide a localization of the site to be approached surgically. A normal myelogram thus deprives the surgeon of a valuable piece of information since the lesion affecting the spinal cord may not lie in the immediate vicinity of the bone defect. In some of our cases with a normal myelogram we have been able to operate and find a lesion only because the pattern of spina bifida resembled that occurring in a case previously explored and thereby suggested the likely site and the type of lesion to be anticipated.

All our investigated cases except one have spina bifida occulta, varying in degree from the barely noticeable to the very extensive. The one case with no bone anomaly shown on a radiograph had a normal myelogram; the short leg and pes cavovarus show no further deterioration in the last 12 months and there is no neurological deficit. This child has not been operated on.

As we have already pointed out (James and Lassman, 1958), there is no published information about the normal level in the vertebral canal of the conus medullaris during the years between birth and full growth although we have post mortem evidence suggesting that the ascent of the spinal cord is normally completed by the end of the fifth year of life. Where myelography can demonstrate the level of the conus and when this can be regarded as abnormally caudal, there can also be assumed to be a traction lesion which should be dealt with surgically. Many of these traction lesions will show no other abnormality on myelography and they are the most difficult to diagnose and to localize. Tomography can be of assistance in some cases, notably those with a bone septum in diastematomyelia and those with inversion of laminae where the demonstration of the size and locality of bone anomaly assists the surgeon in the planning of the

operation which must, of course, involve as few laminae as possible. Only two of our cases needed excision of four pairs of laminae; the remaining eight had three pairs removed.

Pain has not been a factor in the symptomatology of our cases, nor has the spasticity reported by other writers, and this is possibly because we have been able to see our cases at an earlier stage in their history. Neither has ataxia in the form of clumsiness and unsteadiness been evident (except in Case 2), but it is obviously likely to occur at a later stage. Low back pain or stiffness occurring on getting up in the morning and passing off with activity has been referred to by other authors but has not been complained of in our series. The two most important early clues to indicate a possible lesion affecting the spinal cord or cauda equina are either a short leg and foot or a circulatory defect of the skin of the lower limb (as in Cases 5 and 2) of the type seen following poliomyelitis and associated with spina bifida cystica (see also case reported by James and Lassman, 1958).

We wish to stress again the importance of investigating any statement by the parents as to causation of the deformity. Just as other clinicians have done, we have seen many cases where a deformity has had to be considered as due to poliomyelitis because no other cause appeared to be likely; this diagnosis has naturally been passed on to the parents in spite of the absence of any other real evidence of this infection in the past. Injury also has often been advanced by the parents as their own idea of the cause; it is surprising how many children have been dropped in infancy. One adult found to be affected attributed the foot deformity to an injury caused at the age of about 1 year, when her forefoot had caught under a door. She and her family had been satisfied to accept this explanation ever since. Her left foot was normal but the right foot had markedly diminished sensation, pes cavus, clawed atrophic toes and trophic ulceration. Her right leg was $\frac{1}{2}$ in. short. She had two hairy patches on her back and radiographs showed congenital anomalies of the lower lumbar spine and sacrum. The few adult cases we have seen have not been investigated to the extent of myelography. Their deformities, neurological deficits and trophic lesions have been in existence too long to be likely to benefit by laminectomy. They have been treated as conservatively as possible in the same way as cases of spina bifida cystica.

It is clear that the types of abnormality associated with occult spinal cord lesions are similar to those associated with overt spinal cord lesions, although the severity of the physical disability in the latter is

usually much greater. The essential difference between the two types of lesion of the spinal cord is that the occult lesion is usually extrinsic, whereas the overt lesion is an intrinsic lesion of the spinal cord itself. The latter is therefore much more severe and results not only in failure of spinal cord development but also in failure of formation of normal tissues which should be developing synchronously with the spinal cord. The extrinsic lesion occurs slightly later in foetal development; there may be no associated failure in other tissues and its principal effects occur with growth of the child after the associated tissues have been formed; the subsequent abnormalities therefore develop gradually and later in life. As has already been indicated in the syndrome we have described, the established deformity of pes cavo-varus resembles a type of relapsing club foot. If the extrinsic lesion of the spinal cord were to have an effect *in utero*, the pes cavo-varus would possibly have the appearance at birth of a typical club foot because the muscle imbalance would have started earlier and would have been able to advance more rapidly. After birth there are restraints upon this muscle imbalance by the establishment of coordinating reflexes and by the decreasing plasticity of the bones of the foot which provide a mechanical obstruction.

In this communication we have made statements which are based on facts and experience; we have avoided theory as far as possible, but as we continue our clinical and surgical investigations we believe that it may be possible to classify some types of foot deformity as being caused by occult spinal cord lesions. Some cases of club foot are associated with meningocele but the aetiology of other cases is still unknown, and it seems possible that some of the other cases which relapse repeatedly and necessitate local surgery may be due to an occult spinal lesion of the type which we have described here.

The well known association of pes cavus and spina bifida occulta may possibly be now explained but all cases of pes cavus do not necessarily fall into this class and there is obviously need for a reclassification by specifying with greater care the exact form of the pes cavus.

Sufficient information has been obtained to conclude that it is possible to diagnose these cases early and to perform preventive laminectomy without waiting for foot deformity to become fixed. Case 5 demonstrates that with such early procedure muscle balance can become normal or nearly so. Altered bone shape in the older child resulting from abnormal muscle action cannot return to normal but in the very young child almost complete recovery

in this respect may be possible with the return of normal muscle function.

Summary

The purpose of this communication is to emphasize that many types of spinal lesion which have been reported individually are different manifestations of spinal dysraphism and that it is important to recognize their common pattern of symptoms and signs so that an early diagnosis can be made and further deterioration and disability prevented by surgical removal of the cause.

The spinal lesions are classified in three groups, as traction lesions, pressure lesions and combined (traction and pressure) lesions. One case of each type of lesion, proved by operation, is described.

The symptoms and signs facilitating early diagnosis in childhood are discussed. The commonest and earliest evidences are shortening of one foot and leg or circulatory deficiency of the skin of the legs.

The progression of the syndrome by stages to severe neurological deficit, to deformity of the lower extremities and possibly to paraplegia is also described.

The necessity for myelography as a diagnostic procedure is indicated and its uses are discussed.

It is valuable as a preliminary to laminectomy in demonstrating not only the nature of the lesion but also its site. A normal myelogram does not exclude the presence of a lesion. Laminectomy as a method of treatment can be expected only to halt the progressive deterioration. In some cases, however, partial recovery will occur, but such a possibility can only be hoped for and the main purpose of operative treatment is to prevent further disability.

We are indebted to Dr. Gordon Gryspeerdt, Neuro-radiologist and to Dr. Douglas Whitby, Anaesthetist, for their most helpful collaboration in the diagnosis and treatment of our patients and also to our colleagues, Dr. George Davison and Dr. Christine Cooper, in the Paediatric Department of the Newcastle General Hospital. The photographs and reproduction of the x-ray films were produced by the University Department of Photography, King's College, Newcastle upon Tyne.

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CORTICAL ATROPHY OF THE BRAIN IN INFANTS ASSOCIATED WITH FAILURE TO THRIVE

BY

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Infants may fail to thrive for a variety of reasons. When recognized causes such as congenital abnormalities, infections, defective intake and absorption, metabolic and endocrinal disturbances have been excluded, there still remains a group in which no satisfactory explanation is readily apparent. One cause which may account for some of these marasmic infants, and which does not appear to have been previously recorded, is cortical atrophy of the brain. Attention was drawn to this possibility by finding a hemiplegic infant who would not gain weight. An air encephalogram (A.E.G.) revealed cortical atrophy of the brain. Subsequently A.E.G.s were done on other infants, even if they had no clinical signs of damage to the nervous system. In all of them, unless stated to the contrary, the urine, chest radiograph, Mantoux test, Wassermann reaction, blood urea and serum chemistry were normal. Air encephalograms were only done if, after two months of adequate diet in hospital, there was no satisfactory reason found for the failure of these infants to gain weight.

Lumbar A.E.G.s were done under sedation with seconal and largactil. Spinal fluid was replaced by an equivalent volume of air. The total volume of air varied from case to case, but in no child was an excessive amount injected, nor was there any increase in intracranial pressure as judged by bulging of the fontanelle during or following the procedure. No ill effects following A.E.G. were seen in any of the infants.

Case Histories

Case 1. V.W., aged 4 months, was admitted on November 28, 1955, weighing 6 lb. 7 oz. Birth weight was said to be 3 lb. 3 oz. The only abnormal physical signs elicited were a mild right spastic hemiparesis and a head circumference of 13.25 in. A radiograph showed two well-developed centres of ossification in the carpal bones. Eleven weeks after admission the child weighed 6 lb. 15 oz. A.E.G. showed some ventricular dilatation

and excessive cortical air suggesting atrophy. By the age of 2 years 9 months the child had grown fairly well, her head circumference was 17.75 in., but the hemiplegia was marked and she had difficulty in speaking.

Case 2. C.P., aged 6 weeks, was admitted on February 7, 1956, weighing 7 lb. 6 oz. Labour and pregnancy were normal. The infant sucked poorly, vomited intermittently and failed to thrive. Fifteen weeks after admission she weighed 7 lb. 5 oz. A barium swallow and meal revealed nothing abnormal. She was somewhat slow in her development but had abnormal neurological signs. An A.E.G. at the age of 6 months was only contemplated because of the findings in Case 1. It showed excessive cortical air compatible with atrophy.

Case 3. S.G., aged 7 months, was admitted March 17, 1956, weighing 9 lb. 6 oz. The pregnancy had been normal but the infant had been born by breech delivery. The child sucked poorly. She had a bronchopneumonia and it was noted that she could not sit. She was re-admitted at 10 months, weighing 11 lb. 10 oz., because of vomiting and failure to thrive. A barium meal showed a hiatus hernia. Vomiting improved somewhat on medical treatment but at a year she still could not sit unsupported. There were no abnormal neurological signs except occasional spasms of the eyes of an oculogyric type. The head circumference was 16 in. Eleven weeks after admission she weighed 11 lb. 14 oz. An A.E.G. showed gross evidence of cortical atrophy. Follow-up at 3 years 9 months found the child to be mentally very retarded, weighing 20 lb. 6 oz. and with a head circumference of 18 in.

Case 4. J.V., aged 1 year, because of failure to thrive, was admitted on September 18, 1957, from the Skin Ward where she was under treatment for eczema, hepatosplenomegaly and anaemia. She weighed 9 lb. 14 oz. The head circumference was 14.5 in. She had nystagmus and could not hold up her head. The serum cholesterol, bone marrow and a radiograph of the long bones were all normal. A.E.G. showed evidence of gross cortical atrophy and ventricular dilatation. The child died weighing 8 lb. 2 oz.

Case 5. A.L. was admitted on September 16, 1957, also from the Skin Wards, where she had been found to be suffering from ectodermal dysplasia. The blood urea varied between 56 and 72 mg./100 ml. An intravenous pyelogram showed a normal pattern on the right side and delayed secretion from the left kidney. The child gained 12 oz. in weight in 8 weeks, and at 7 months weighed 8 lb. 12 oz. An A.E.G. showed some ventricular dilatation and gross cortical atrophy.

Case 6. S.J., aged 2 weeks, was admitted on June 10, 1957, weighing 5 lb. 11 oz. Labour and pregnancy had been normal. There was frequent vomiting and at the age of 12 weeks she weighed 5 lb. 15 oz. Subsequent weight gain was slow. An A.E.G. at 5 months showed cortical atrophy as well as some subdural air.

Case 7. V.M., aged 2 weeks, was admitted on December 30, 1957, weighing 3 lb. 3 oz. She had had a minor convulsive episode on the third day of life. The first 8 months of life were spent in hospital during which time she gained weight slowly. She could then hold up her head but could not sit even with support. Both optic discs were pale but she could see and followed objects without making any effort to grasp. A radiograph showed three carpal centres of ossification. An A.E.G. at 8 months showed slight ventricular dilatation and cortical atrophy. A carotid angiogram was done on the right side and showed a normal anatomy of the cerebral vessels. The child died when 16 months of age, weighing 10 lb.

Interpretation of Air Encephalograms

Smith and Crothers (1950) have emphasized the need to interpret, with reserve, air shadows lying over the brain cortex. The common error is to

diagnose cortical atrophy because air has entered the subdural space. Subdural air can be recognized by the following features: (1) It moves with alteration of posture of the head. (2) It dips down beside the falx and along the tentorium cerebelli (see Fig. 1). (3) It is smoothly lined and is associated with fluid levels (Fig. 2).

Cortical atrophy can be recognized in the following way: (1) The frontal and parietal regions are predominantly affected (Fig. 3). (2) It produces an irregular picture of peaks and valleys the dilated sulci being usually more than 3 mm. wide (Figs. 4 and 5). (3) If the picture is associated with ventricular dilatation it is diagnostic, but it must be stressed that considerable atrophy of the cortex can occur and yet the ventricles may appear to be normal in size.

Judged by these criteria, all cases in this series had cortical atrophy. It is recognized, however, that a positive diagnosis of brain atrophy based solely on the A.E.G. appearances is not justified. All the infants were at an age when normally rapid brain growth occurs and the changes seen on A.E.G. might have been in part, if not wholly, due to a primary defect in growth rather than an atrophy. No separation of the two types of defect is possible on the evidence available, and in this paper the term atrophy may in fact be covering both a primary defect in cerebral growth and atrophy due to brain damage.

Three facts seem to confirm the diagnosis of cortical atrophy made from these A.E.G.s. Firstly, in those children who have survived and have been followed up, if it was not obvious at first, there has been subsequent clear evidence of brain damage. Secondly, the A.E.G.s of those children with clinical evidence of brain damage differed in no way from those who showed no clinical evidence of damage to the nervous system at the time of A.E.G. Thirdly, confirmation of cortical atrophy was found at necropsy in two other children who had similar A.E.G. changes, but who are not included in this series as their physical development was normal.

It must be stressed that the presenting symptom in these infants was failure to thrive. In Cases 2, 6 and 7 the possibility of cortical brain damage was not at first suspected. These infants were still very young and it was thought that any slowness of intellectual development could be accounted for



FIG. 1.—Subdural air: showing extension along the tentorium cerebelli.



FIG. 2.

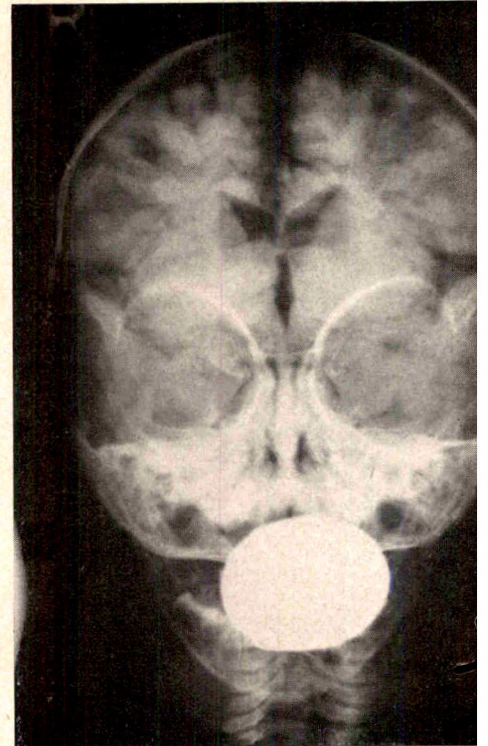


FIG. 4.

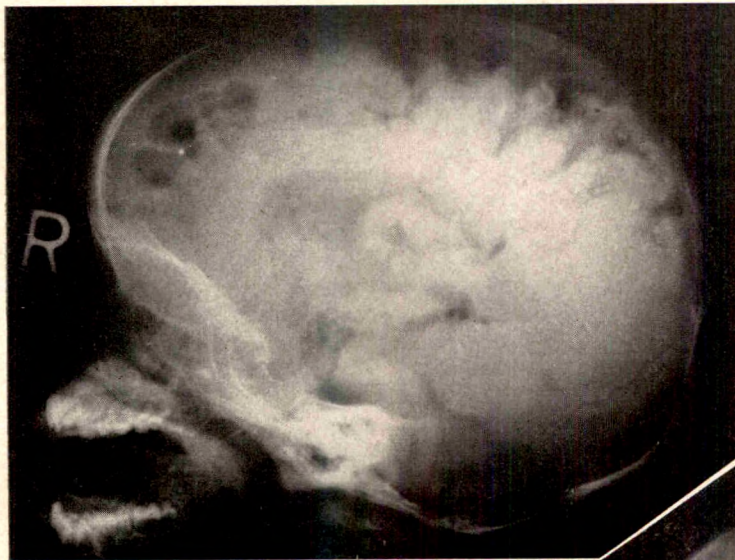


FIG. 3.

FIG. 5.



FIG. 2.—Subdural air: showing a fluid level.

FIG. 3.—Cortical atrophy: showing predominantly parietal involvement.

FIG. 4.—Cortical atrophy: A.P. view showing widening of the sulci.

FIG. 5.—Cortical atrophy: lateral view showing widening of sulci.

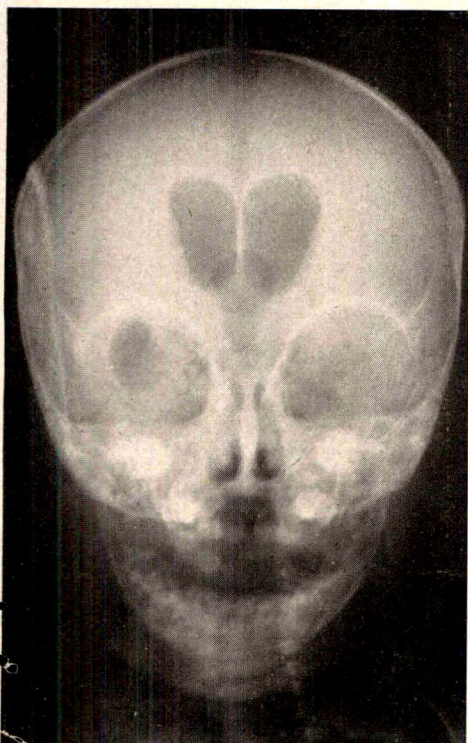


FIG. 7.

FIGS. 6 and 7.—A.E.G.s to show the contrasting picture of dilatation of the ventricular system following pyogenic meningitis.

FIG. 6.

by the failure of physical growth. Only later, after the infants had been followed for some months, was it realized that the cerebral damage was probably the basic abnormality. Cases 1 and 3 differed from the others only in that they had neurological signs which drew attention to the brain damage. Involvement of areas of the brain that produce definite abnormal physical signs does not, however, seem to be an adequate reason for separating this group from those with no neurological signs. In Cases 4 and 5 there was associated disease that probably contributed to, if it was not the major cause of, the failure to gain weight. Their inclusion seems justified as they showed a similar clinical state and the same changes on their A.E.G.s.

One can only speculate on the cause of the atrophy. There was no familial incidence to suggest a genetic factor. In only one infant was an arteriogram done and this showed no evidence of a vascular defect. It is most unlikely that the cause was a meningitis. Some history of a previous illness should have been obtainable. Furthermore, A.E.G.s done on infants who have had meningitis show an entirely different picture with dilatation of the ventricular system, very little if any air over the cortex and rarely any subdural air (Figs. 6 and 7).

In fact the readiness with which the ventricles of children, who have had meningitis, fill, suggests that some other factor plays a part, and that this is possibly dilatation of the whole of the ventricular system including the aqueduct which allows a freer efflux of ventricular fluid and its replacement with air. The atrophy is most likely to be the result of cerebral anoxia, probably intra-uterine or neonatal. Frontal and parietal involvement occurs frequently in such circumstances, and the small size of the heads of these infants also supports the concept of the damage occurring at an early age.

There are many factors governing normal growth and in general growth may be impaired for three main reasons: (1) when diet fails to supply the required nutrients; (2) when there is some breakdown in the physiological process of transporting the nutrients to the tissues; and (3) when the body fails to utilize the nutrients.

Keys (1953) believes that the only neurological causes of failure to thrive are those diseases causing loss of appetite, and those neurological lesions which interfere with feeding. At present no neurological 'centres for growth' are known. Brobeck (1946) states that the hypothalamus normally participates in the maintenance of the overall energy equilibrium

and Brock (1953) ascribes this function to the thalamic hypothalamic level. Lesions of the pituitary might be expected to show delayed ossification of the centres of bone growth. In those children of this series where radiographs of the carpus had been taken, the bone age appeared normal. After damage to the frontal lobes, both clinically and experimentally, a weight loss is frequently observed. Because these subjects frequently manifest voracious appetites, this loss of weight has been ascribed to hypermobility of the intestinal tract (Fulton, Jacobsen and Kennard, 1932). The converse also applies, and a great diminution in appetite, depending on altered prefrontal cortical function, has been described (Brock, 1953). Thus the prime effect of neuronal damage has been an alteration in the hunger drive, with only a secondary nutritional effect. In three of the infants of this series, vomiting apparently of a cerebral type, must have affected growth although it did not always appear either severe or frequent enough to be an entirely satisfactory explanation for the failure to gain weight. In two others there was no vomiting, feeding was normal and appetites were reasonable. When there was some impairment of appetite, tube feeding still failed to achieve a reasonable weight gain. This would suggest that, in some children, cortical atrophy through some subtle mechanism has an adverse effect on the general metabolism resulting in a failure to thrive. The fact that other children with clinical and A.E.G. evidence of cortical atrophy had normal physical development raises the possibility of there being some 'centre for growth' which is affected in some cases and not in others.

In conclusion, it is recognized that the diagnosis of cortical atrophy of the brain is easily made as these infants grow older; but it would be helpful to know the cause of failure to thrive in very young infants when the recognition of mental retardation is not so easy; parents and doctors can then be spared a period of uncertainty as to the nature of the child's illness. In addition unnecessarily prolonged hospitalization can be avoided in those hospitals where there is still a tremendous pressure on beds.

Summary

A series of infants is described in which failure to thrive was the presenting symptom. All of them had heads that were small in circumference and, if not apparent when first seen, subsequently showed evidence of marked mental retardation. All of them had abnormal air encephalograms which were interpreted as indicating cortical atrophy of the brain. In infants the association of cortical atrophy of the brain with failure to thrive does not appear to have been previously recorded.

We wish to thank Professor F. J. Ford for help with the paper; Dr. J. A. Burger, Medical Superintendent of Groote Schuur Hospital, for permission to publish and Mr. Todd for the photographic reproductions.

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THE INCIDENCE OF TWINS IN CEREBRAL PALSY AND MENTAL RETARDATION

BY

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There is evidence that there is a higher incidence of mental retardation and of cerebral palsy among children born from a multiple pregnancy than among singletons. Asher and Schonell (1950) found that 5.4% of their 400 cases of cerebral palsy were members of twins. Greenspan and Deaver (1953) found that 7% of their 94 cases resulted from multiple pregnancies. The corresponding figure in Shyh-Jong's series of 301 cases (Yue, Shyh-Jong, 1955), was 9.0%.

Loofft (1931) found a higher incidence of imbeciles in a group of 64 twins than one finds in the normal population, and among siblings and parents of backward children there were more twins than among normal children. Rosanoff and Inman-Kane (1933) studied 234 pairs of mentally defective twins. They found a higher incidence of mental defects in twins than in singletons. McKinney, Dunphy and Pessin (1958) and Drillien (1959) made similar observations. The latter, in her follow-up of the intelligence quotient of premature babies, found that twins scored less than singletons.

It is not easy to interpret these observations, on account of the higher incidence of cerebral palsy with or without mental retardation, and of mental retardation alone, in prematurely born children, and the high incidence of prematurity in multiple pregnancy.

One could not say, therefore, whether the high

incidence of twins in children with mental retardation or with cerebral palsy is merely due to the high incidence of prematurity associated with multiple pregnancy. We therefore set out to elucidate the matter.

An analysis of mentally retarded children or children with cerebral palsy seen at the Children's Hospital, Sheffield did not provide sufficient material for satisfactory statistical conclusions to be made. Accordingly, Dr. Grace Woods of Bristol was asked to cooperate by supplying figures from her large series seen at the Cerebral Palsy Assessment Clinic at the Bristol Children's Hospital (in the case of cerebral palsy), and at a mental deficiency hospital, a mental health clinic and an occupation centre. The Department of Medical Statistics, at the University of Sheffield, analysed the figures.

We made no attempt to distinguish identical from non-identical twins owing to the difficulty of distinguishing these without such accurate methods as the study of blood groups.

The Statistical Problem

The Table sets out the basic data, from which it can be seen that of 729 mentally retarded children, including mongols, 153 (20.9%) were prematurely born, as compared with 234 of 651 children with cerebral palsy (35.9%); of 729 mentally retarded children including mongols, 28 were members of

TABLE
INCIDENCE OF PREMATUREITY AND TWINS IN MENTAL RETARDATION AND CEREBRAL PALSY

	Mental Retardation excluding Mongolism or Cerebral Palsy			Mongols			Cerebral Palsy		
	Sheffield	Bristol	Total	Sheffield	Bristol	Total	Sheffield	Bristol	Total
Premature singletons	68	40	108	16	11	27	76	115	191
Full term singletons	274	188	462	46	58	104	155	250	405
Premature twins	8	6	14*	2†	2	4	12	31	43§
Full term twins	3	6	9†	1	0	1	9	3	12
Total	353	240	593	65	71	136	252	399	651

* Four premature twins were siblings.
† Six full term twins were siblings.

‡ Two premature twins were siblings.
§ Four premature twins were siblings.

twins (3.8%), as compared with 55 of 651 cases of cerebral palsy (8.4%).

Our studies showed that of 375 consecutive premature births in two Sheffield hospitals, 44 children (11.2%) were members of twins (Dr. Ronald Gordon kindly supplied figures for the City General Hospital, Sheffield. The remaining figures were from the Jessop Hospital for Women), and of 252 consecutive twins in the two Sheffield hospitals, 145 (57.7%) were 'premature', weighing 5½lb. (2,500 g.) or less. The incidence of twins in the normal population was taken as 1.2% and the incidence of prematurity as 6.0%.

Results of Statistical Analysis. The high incidence of twins in cerebral palsy is not merely a reflection of the high incidence of prematurity.

The high incidence of twins in mentally retarded children may well be due merely to the high incidence of prematurity.

Discussion

The reason for the high incidence of multiple pregnancy in the history of children with cerebral palsy is unknown. The factors concerned may be partly genetic and partly obstetrical, multiple preg-

nancies being associated with a high incidence of abnormal presentations and deliveries. The evidence for a genetic factor in some cases of cerebral palsy has been set out elsewhere (Illingworth, 1958).

Summary

We set out to determine whether the high incidence of twins in children with cerebral palsy and with mental retardation without cerebral palsy is merely due to the high incidence of prematurity associated with multiple pregnancy. Statistical analysis has shown that in the case of cerebral palsy the high incidence of twins is not explained by the high incidence of prematurity which is known to be related to cerebral palsy. In the case of mentally retarded children without cerebral palsy the high incidence of twins may well be merely related to the high incidence of prematurity known to be a factor in mental retardation.

Of 729 mentally retarded children without cerebral palsy, 20.9% were prematurely born and the incidence of twins was 3.8%. Of 651 children with cerebral palsy, 35.9% were prematurely born, and 8.4% were twins.

Statistical Addendum

BY

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Estimates of the main probabilities required for a test of significance on the data in Table 1 are given in Table 3. These have been deduced from the facts given in Table 2 using the method of weighted least squares to resolve the inconsistencies of the latter. In doing this, the following points have been borne in mind:

- (1) The first two figures of Table 2, though rough,

TABLE 2

INCIDENCE DATA FOR PREMATUREITY AND MULTIPLICITY

Incidence of twins in normal population:	1.25%
Incidence of prematurity in normal population:	6%
Incidence of twins among 375 consecutive premature births in two Sheffield hospitals:	11.7% (44 children possibly 22 pairs)
Incidence of prematurity among 252 consecutive twins:	57.6% (145 cases)

TABLE 1

DISTRIBUTION OF CASES ACCORDING TO PREMATURE AND MULTIPLE STATUS FOR DIFFERENT CONDITIONS (BRISTOL AND SHEFFIELD)

		Premature Singletons	Full term Singletons	Premature Twins	Full term Twins	Total
Cerebral palsy	Sheffield	76	155	12	9	252
	Bristol	115	250	31	3	399
	Total	191 (29.3%)	405 (62.2%)	43 (6.6%)	12 (1.8%)	651
Simple mental defectives	Sheffield	68	274	8	3	353
	Bristol	40	188	6	6	240
	Total	108 (18.2%)	462 (77.9%)	14 (2.4%)	9 (1.5%)	593
Mongol idiots	Sheffield	16	46	2	1	65
	Bristol	11	58	2	0	71
	Total	27 (19.9%)	104 (76.5%)	4 (2.9%)	1 (0.7%)	136

have been treated as firm values, i.e. free from statistical error due to paucity of cases.

(2) The standard errors of the other two figures have been assessed from the binomial distribution, taking the birth of a pair of twins as a single random event.

As a preliminary, the mutual compatibility of the Bristol and Sheffield figures in Table 1 was examined by means of χ^2 tests (3 D. of F.) for each of the three conditions. The values were 9.03 (cerebral palsy), 3.23 (simple mental deficiency), 2.24 (mongol idiots); of these the first was significant, on the 5% level only, the other two being not significant. The significance was mainly due to the somewhat smaller percentage of full term twins in the Bristol figures, and was not considered important enough to prevent the two sets of figures being lumped together for further analysis.

TABLE 3
PROBABILITIES OF PREMATURITY AND MULTIPLICITY
FROM DATA IN TABLE 2

	Estimated Probability (%)
Premature singleton	5.28
Full-term singleton	93.47
Premature twin	0.72
Full-term twin	0.53
Total	100.00

NOTE.—The second decimal is given to avoid accumulation of rounding off errors in working.

Since the incidence of twins is small, the number falling into any given category can be taken as a Poisson variate, provided that only one of a pair of siblings is included in the count. Also since Poisson variates are additive, results for premature and full term children may be added for the purpose of a test of significance. These two considerations lead

TABLE 4
OBSERVED AND EXPECTED INCIDENCE OF TWINS FOR
DIFFERENT CONDITIONS

	Observed Number	Expected Number	Significance of Discrepancy
Cerebral palsy	54	30.3	0.1% level. Not significant even on 5% level
Simple mental defectives	20	17.2	
	24	21.4	
Mongol idiots	4	4.2	

to Table 4, the significance of the discrepancies being assessed by reference to the Poisson tables; the expected numbers are deduced by applying the incidence rates of Table 3 to the numbers of premature and full term cases at risk in the various categories. No allowance has been made for statistical errors in the expected numbers arising in their derivation from the data in Table 2, and thus will tend to lead to a slight overstatement of the level of significance; notwithstanding this, the results are clear enough for there to be no doubt of the *significantly greater incidence of twins among cases of cerebral palsy*. On the other hand, there is no evidence of an abnormal incidence of twins in the presence of either of the other conditions.

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CONVULSIVE MOVEMENTS OCCURRING IN THE FIRST 10 DAYS OF LIFE*

BY

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It has been estimated that approximately 6% of children under the age of 5 years have convulsions due to one cause or another. Moreover, it is generally recognized that this liability to convulsive incidents is greatest in infancy. There is little mention in the literature of the extent to which these generalizations apply to the early days of life, although it is well known that convulsions in newly-born infants occur in a wide variety of circumstances. I present here the results of a study of convulsions occurring for the first time within 10 days of birth.

The Clinical Material

Three hundred and seventy-five babies are included in the study, of whom 158 died and came to autopsy, and 216 survived the neonatal period. With a few exceptions the infants were born in the Simpson Memorial Hospital, Edinburgh, or the Maternity Hospital, Leeds. The exceptions had been delivered elsewhere and subsequently transferred to one or other of the above-mentioned hospitals. All 374 babies were seen personally and were under continuous clinical supervision for a period of not less than 10 days unless death intervened.

Fatal Cases (158): Pathological Findings

The pathological findings in the 158 fatal cases are analysed in Tables 1 to 5. Significant non-infectious intracranial pathological changes were present in almost two thirds of the babies. Infection, developmental anomalies and haemorrhage (other than intracranial) were present in that order of frequency in the remaining fatal cases. Findings were completely negative at nine autopsies (Table 1).

There was evidence of intracranial infection (Table 2) in 18 and of septicaemia without intracranial involvement in seven babies. Infection was

TABLE 1
CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: MAJOR AUTOPSY FINDINGS

Infection	29
Developmental anomalies .. .	14
Acquired (non-infectious) intracranial pathology ..	97
Haemorrhage other than intracranial .. .	9
Nil	9
	158

coliform in nine, streptococcal (haemolytic) in two, pneumococcal in one and staphylococcal in two of the 14 babies with septicaemia and meningitis. Blood obtained during life from the seven infants with septicaemia without meningitis gave cultures of *Esch. coli* in four, *Staphylococcus aureus* in two, and streptococcus in one. The strain of streptococcus was not established. Of the four cases of otitis media three were the result of pneumococcal and one of staphylococcal infection. Pyelonephritis was associated with coliform infection in two babies and with *Staphylococcus aureus* infection in one. The primary focus in babies with staphylococcal infection was in the eye in one, the ears in one and the skin in four cases, the majority of which occurred before the advent of antibiotic therapy. Neither brain nor meninges was the site of pathological changes in the babies with pyelonephritis and congenital syphilis.

With regard to deaths contributed to by developmental anomalies (Table 3) the three examples of

TABLE 2
CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: DEATHS DUE TO INFECTION

Septicaemia with meningitis .. .	14
Septicaemia .. .	7
Otitis media with secondary meningitis .. .	3
Pyelonephritis .. .	3
Otitis media with secondary brain abscess .. .	1
Congenital syphilis .. .	1
	29

* Based on lectures given at the University of Bergen and to the Medisinsk Selskap, Oslo.

internal hydrocephalus all occurred in small premature infants. The renal and cardiovascular abnormalities were of a major character and incompatible with survival. Infants with evidence of cerebral agenesis are referred to later.

TABLE 3
CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: DEATHS CONTRIBUTED TO BY
DEVELOPMENTAL ANOMALIES

Cerebral agenesis	6
Internal hydrocephalus	3
Cardiac with associated transposition of great vessels	2
Hydronephrosis (with secondary infection)	2
Cystic kidneys	1
	14

Haemorrhage contributed to death in a variety of ways (Table 4). Massive intrapulmonary haemorrhage was a feature in two cases, in one of which there was microscopical evidence of early secondary staphylococcal infection. Of the two examples of fatal exsanguination one was the result of incision of the placenta in the course of delivery by caesarean section and the other of massive intestinal haemorrhage in a baby with untreated haemorrhagic disease who had been born outside hospital. All the examples of suprarenal haemorrhage were massive and associated with widely distributed tardieu spots. In none of the cases was there a history of trauma or evidence of infection and I cannot say whether the suprarenal haemorrhages were the cause or the result of associated asphyxia. Suprarenal haemorrhage certainly was the immediate cause of death in each case.

TABLE 4
CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: DEATHS CONTRIBUTED TO BY
HAEMORRHAGE OR CONGESTION

Intrapulmonary haemorrhage	2
Exsanguination	2
Suprarenal haemorrhage	5
Intracranial haemorrhage, venous congestion or oedema	97
	106

Haemorrhage within the cranium was found in a number of different situations (Table 5). In many instances post mortem findings pointed to asphyxia having been secondary to traumatic haemorrhage. In an equal number it was not possible to differentiate the relative aetiological significance of coexistent haemorrhage and asphyxia. This was especially true of a high proportion of infants with subarachnoid and intraventricular haemorrhage. In two infants intracranial haemorrhage was associated with bleeding into the peritoneal, pleural and pericardial sacs which was

regarded as evidence of haemorrhagic disease; and in one baby bleeding arose from septic thrombosis of the choroid plexus in the presence of staphylococcal septicaemia without meningitis. Aseptic thrombosis of the choroid plexus with secondary intraventricular haemorrhage was found in six babies all of whom were markedly premature and died after the tenth day of life. In two of these babies there was, in addition, thrombosis of the renal vessels and in one, dry gangrene of the toes secondary to thrombosis.

Severe generalized venous congestion or extensive oedema was the only finding in about 15% of the fatal cases with acquired non-infectious intracranial pathology.

Pneumonia was present in 13 of the infants coming to autopsy, but was considered to be a terminal complication in each instance.

TABLE 5
CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: ACQUIRED (NON INFECTIONOUS)
INTRACRANIAL CONDITIONS

Haemorrhage: subdural	30
subarachnoid	14
intraventricular	23
multiple perivascular in brain substance	6
Venous congestion involving meninges and brain substance	9
Generalized oedema	7
Sinus thrombosis	4
Kernikterus	4
	97

Surviving Cases (216): Diagnoses

Surviving cases are best considered according as the clinical diagnosis was proven, being confirmed by appropriate laboratory studies, or was conjectural, being based upon clinical observations.

Proven Diagnoses. Table 6 lists the 38 cases in which a firm diagnosis was made. Infection was present in 15. Pyelographic investigations were not considered desirable or practicable in the cases of urinary infection. The possibility of renal abnormalities in these cases was not therefore excluded, but none of the infants concerned had a recurrence of signs or symptoms by the age of 2 years. Exsanguination resulted in one infant from prolonged, severe intestinal bleeding due to haemorrhagic disease, and in the other infant was thought after examination of the mother's blood to be due to foetal intraplacental haemorrhage. Both infants were born at home and there was delay in diagnosis and treatment. The patients with cerebral agenesis are described later. Convulsions started on the tenth day of life in each of the babies with subdural effusions. The fontanelle

TABLE 6
CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
SURVIVING BABIES: PROVEN DIAGNOSES (38)

Diagnosis	Confirmation	No. of Cases
Meningitis: <i>Esch. coli</i>	Bacteriological	3
Pneumococcus	Bacteriological	2
Meningococcus	Bacteriological	1
<i>B. friedlander</i>	Bacteriological	1
<i>Proteus</i>	Bacteriological	1
Pyelonephritis	Cytological:	
	Bacteriological	7
Exsanguination	Clinical, haematological and therapeutic	
Cerebral agenesis	Air encephalography	11
Subdural effusion	Aspiration:	
	Air encephalography	2
Kernikterus	Serological and biochemical	6
Tetany	Biochemical	2

was a little tense and the resistance on percussion of the two sides of the cranium differed. A tentative diagnosis leading to confirmatory aspiration was not made until some weeks later by which time convulsions were recurring at intervals of several days. In the two infants with tetany, convulsions occurred as the culmination of particularly exhausting periods of severe generalized neuromuscular hyperexcitability and coincided with depression of the serum calcium level below 6 mg./100 ml. Both babies were the offspring of mothers with diabetes mellitus (Craig, 1958).

Presumptive Diagnoses. The presumptive diagnoses in 178 surviving infants are given in Table 7. In over 80% of these babies the diagnosis was intracranial disturbance. This term is used deliberately as it is only rarely possible to differentiate clinical signs of intracranial disturbance during life due to cerebral haemorrhage, congestion and oedema. It might be argued that lumbar puncture would have assisted in differential diagnosis. In my opinion this is open to question and lumbar puncture should be reserved for those cases in which the need arises to exclude meningitis. Potter (1952) draws attention to the limited value of examination of the cerebrospinal fluid as a diagnostic measure in cerebral haemorrhage.

With regard to other cases included in Table 7 the

TABLE 7
CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
SURVIVING BABIES: PRESUMPTIVE DIAGNOSIS (178)

Poliomyelitis	1
?-Aseptic meningoencephalitis	1
Alimentary disturbance (non-infectious)	7
Aspiration of feeds	4
Hypothermia	9
Cold injury	4
Intracranial disturbance	152
	178

diagnosis of poliomyelitis in a baby in whom two isolated convulsions occurred on the tenth day of life was based on a history of contact, a temporary pronounced increase of lymphocytes in the cerebrospinal fluid and a residual flaccid paresis and muscle wasting still present in the left lower limb at the age of 4 years. No convincing explanation of the case labelled '?-aseptic meningoencephalitis' can be offered. There was no clue in the birth history. The child was born at term. Progress was uneventful apart from a succession of violent general convulsions on the eighth day of life and the presence of nuchal rigidity for several days. Cells in the cerebrospinal fluid were greatly increased for a week, lymphocytes predominating, but successive bacteriological cultures were consistently negative. At 3 years of age the child's condition was in every way normal.

Five of the seven cases listed as alimentary disturbance were similar. A violent convulsion in the second week of life in a previously healthy baby occurred simultaneously with the passage of an abnormally bulky stool containing numerous large undigested curds. The association between convulsion and manifestly abnormal stools was inescapable. Convulsion and stool were completely isolated incidents. There was neither forewarning nor aftermath. The other two infants in this group were very small premature babies in whom the initial expulsion of meconium was delayed until the sixth day of life due, it was considered, to lack of muscle tone. There was no question of meconium ileus or mucoviscidosis. Generalized twitching movements appeared on the sixth day and did not recur after the removal of the retained meconium by gentle low colonic lavage. Asphyxial convulsions due to aspiration of feeds were due to a lapse in nursing technique in the case of one infant; to difficulty in feeding another baby with a suspected but at the time undemonstrated high, short tracheo-oesophageal fistula; and to injudiciously repeated feeds given to two infants with undiagnosed oesophageal atresia.

Use of the term hypothermia in Table 7 implies that a rectal temperature below 95° F. persisted for a period of not less than 24 hours. Hypothermia was a feature also of the four babies with cold injury, being associated with the hard infiltration of skin, subcutaneous tissues and muscles found in this condition which is variously, confusingly and frequently incorrectly referred to in the literature as sclerema, scleredema, scleroderma and cold injury (Macgregor, 1960). For the purposes of this paper the term cold injury is employed throughout.

Details Concerning Convulsions

The clinical characteristics of convulsions seen in the course of the present study varied considerably. Examples were seen of a tonic phase followed in succession by clonic movements and unconsciousness; of isolated, prolonged tonic incidents; and of both brief and persistent clonic phases not preceded by tonic or followed by unconsciousness. In some instances the onset of a convulsion was immediately preceded by or coincided with a short and sometimes piercing cry; in others grunting or crying was noted during or at the termination of a phase of tonic. A cry was absent in most cases. Violent generalized convulsions were seen with noteworthy rarity in premature babies. Rhythmic clonic movements were common; involved one or several limbs at any one time; frequently affected different limbs at different times; and were often associated with transient unilateral twitching of muscles at the angles of the mouth or eyes. Associated cyanosis, neck rigidity and opisthotonus were occasional findings.

Convulsions Considered in Relation to Diagnosis.

INFECTIONS. Convulsions in babies with septicaemia or meningitis consisted of fitful phases of subdued clonic movements with irregularly interspersed brief events of apnoea. In some infants these incidents occurred spontaneously and in others only when disturbed. Convulsive movements did not appear until after the third day of life even in infants in whom the obstetrical history suggested that infection had been antenatal. The fact that all the infants concerned were premature and frail probably accounted for the convulsions not being severe. In fatal cases there was no relationship between the clinical picture and the location, the extent or the bacteriological nature of the infective process as seen at autopsy. A feature of white blood cell counts during life was that a severe leucopenia was as common as a pronounced leucocytosis. Convulsions occurring in infants with pyuria were generalized but not severe in character, and commenced before the onset of the swinging temperature characteristic of the condition. They ceased as diuresis increased.

DEVELOPMENTAL ANOMALIES. Convulsions seen in babies with major anomalies of the cardiovascular system and of the kidneys were violent terminal events. The infants with internal hydrocephalus were premature and small, and the convulsions consisted of sporadic twitching movements. In marked contrast, babies with cerebral agenesis presented clinical pictures remarkable for their severity and similarity of pattern. The convulsions

first appeared about the second day of life, thereafter occurring spontaneously at frequent but wholly irregular intervals, and persisted despite large and frequent doses of chloral hydrate and phenobarbitone. Structural asymmetry or unusual configuration of the face or cranium was a feature in a significant number of these infants.

HAEMORRHAGE. The convulsions which took place in the presence of external bleeding were isolated but severe and general in distribution. Those that occurred in fatal cases were terminal events. In the two babies who survived exsanguination the convulsions were similar in character and occurred when the infants arrived at hospital *in extremis*, having been transported without previous treatment over distances exceeding 40 miles. Copious haemoptysis preceded the terminal convulsions in babies with massive intrapulmonary haemorrhage. Convulsions in infants with massive suprarenal haemorrhage at autopsy began suddenly a few hours before death and assumed a violent form even when the baby was small and premature. They were accompanied by collapse and tachycardia and in two cases by sweating of abnormal degree.

INTRACRANIAL DISTURBANCE. Convulsions in babies developing kernikterus were subdued in character, recurred at intervals of widely varying length over a period of days and showed great variability in the parts of the body involved. Cycling movements of the lower limbs and boxing movements of the arms were among other features in these infants. The convulsions in the infants with subdural effusions began in the middle of the second week, were vigorous and general and associated with occasional vomiting. Personal experience suggests that the cases were exceptional in that vomiting attributable to subdural effusion usually precedes convulsions which more commonly first appear after the second week of life.

Consideration of intracranial disturbances presents special difficulties. Among babies with subdural haemorrhage major generalized convulsions were a feature in about 50%. Regardless of their severity and whether they were generalized or localized, convulsions tended to recur over a period of 24-36 hours. They contrasted with convulsive movements associated with other forms of intracranial haemorrhage in the readiness with which they were induced by external stimuli. Progressively deepening cyanosis during life was usually accounted for by pressure exerted on the mid brain by large amounts of blood which had gravitated downwards. There was no constant association between generalized convulsions and the distribution of blood over the cortex. Localized convulsive

movements were seldom explained by the anatomical distribution of bleeding.

Clinical features in babies with subarachnoid haemorrhage lacked the drama of those in cases of subdural haemorrhage. Localized slight convulsive or twitching movements were present in about half the infants with subarachnoid haemorrhage. Generalized convulsions were rare. There was no significant correlation between the extent of the subarachnoid haemorrhage and the severity or localization of the convulsive movements. An unexplained finding was the frequency with which twitching was preceded by abnormal movements of the eyes. Intraventricular haemorrhage is sometimes found unexpectedly at autopsy without any signs of cerebral irritation during life. When they did occur convulsions were dramatically sudden in onset, of extreme violence and accompanied by uncoordinated movements of the eyes and piercing cries of intense cerebral pain. These signs were present in 10 babies, of whom seven died in the first, and three in the second week. In five babies isolated slight twitchings were noted for a few hours before the development of major convulsions. The clinical pictures in the six babies with widely distributed intracranial perivascular haemorrhages were strikingly similar. In all the appearance of convulsions was delayed until the second week. From the time of their onset the convulsions were general, of extreme violence and completely exhausting. Persistent restlessness was characteristic. Death occurred suddenly after a period of wild uncontrollability similar to that sometimes seen in small babies with fulminating encephalitis. I have known only two babies survive after presenting this clinical picture. Both were eventually severely

handicapped, physically and mentally, and both were ultimately ataxic.

During life the clinical pictures presented by infants with severe intracranial oedema at autopsy were indistinguishable from those due to other forms of intracranial disturbance.

HYPOTHERMIA AND COLD INJURY. Convulsions in babies with hypothermia were general but not violent, and although not frequent, occurred at lengthy irregular intervals until the body temperature was raised. Similar findings were encountered in the two babies with cold injury, but it was evident that as the stiffness or rigidity characteristic of the condition increased, fine frequent convulsive movements became more coarse and deliberate.

The Incidence of Convulsive Movements

In one hospital to which admissions are subject to obstetrical selection, and at which detailed clinical notes have been kept over many years, the records suggest that one infant in approximately every 120-125 live births has convulsive movements at some time during the first 10 days of life. The incidence is certainly considerably less, although exact figures are not available, in another hospital, with which I am associated, which is of about the same size and which admits only multiparous and uncomplicated maternity cases.

The incidence of convulsions in relation to certain clinical conditions seen in newly-born babies was also studied. Table 8 summarizes the findings.

The Severity of Convulsive Movements and Long Term Prognosis

A follow-up study was made of 141 of the 152 infants who survived the neonatal period and who

TABLE 8
INCIDENCE OF CONVULSIONS OCCURRING IN THE FIRST 10 DAYS OF LIFE
IN ASSOCIATION WITH CERTAIN CLINICAL CONDITIONS

Clinico-Pathological Group	Number of Infants						% of Infants with Convulsions
	Dying†		Surviving†		Total		
	Convulsions		Convulsions		Convulsions		
	With	None	With	None	With	None	
Cerebral agenesis	6	2	11*	2	17	4	81
Septicaemia and/or meningitis	24	10	8	2	32	12	73
Intracranial disturbance	97	1	152	488	249	489	Less than 33
Renal anomalies	3	11	—	—	3	11	
Kernikterus	4	6	6	4	10	10	50
Severe urinary infection	3	3	7	58	10	61	14
Cold injury	—	3	4	15	4	18	18
Haemorrhagic disease	1	1	2	149	3	150	2
Hypocalcaemic tetany	—	—	2	63	2	63	3
Suprarenal haemorrhage	5	10	—	—	5	10	—
Internal hydrocephalus	3	6	—	—	3	6	—
Intrapulmonary haemorrhage	2	8	—	—	2	8	—

* Six of these infants died in the second year of life.

† Relates to first four weeks of life.

‡ Reliable figures not available.

in the first few days of life had shown convulsive tendencies attributed at the time to intracranial disturbance. Of the 141 babies nine died before the age of 2 years and the remaining 132 were last examined between the ages of 3 and 3½ years. Findings were analysed according as the postnatal convulsions had been violent and general, or transient and slight; and were compared with those in a control series consisting of 488 babies who had had no convulsions but had shown signs of postnatal anoxia and distress, and who were re-examined at or shortly after the age of 3 years (Table 9). The figures do not purport to be statistically accurate but reflect a higher incidence of sequelae in babies with a history of neonatal convulsions than in babies with no such history.

TABLE 9

NEONATAL ASPHYXIA/INTRACRANIAL DISTURBANCE WITH AND WITHOUT CONVULSIONS: SURVIVING BABIES: FINDINGS AT OR OVER THREE YEARS OF AGE

Findings at 3 Years of Age or Over	Neonatal Convulsions Number of Babies		
	None	Prolonged/ Severe	Transient/ Slight
Normal	473	85	45
Physical handicap	6	1	1
*Mental handicap	3	1	1
*Physical and mental handicap	6	5	3
Total	488	92†	49‡

* Does not include children considered to be primary aments.

† Includes 9 babies of birth weight of 5½ lb. or less.

‡ Includes 31 babies of birth weight of 5½ lb. or less.

Discussion

The evidence presented indicates that whereas it has been variously stated that 2-4% of children under 3 years (Green and Richmond, 1954) and approximately 6% under 5 years (Davidson, 1953) have convulsions, considerably less than 1% of babies in maternity hospitals have convulsions within 10 days of birth. This is of interest in view of the greater liability to convulsions of infants as compared with older children (Davidson, 1953) and of the findings of Crump (1945) which show that the incidence of convulsions is lowest in the first six months of life and highest between the ages of 6 months and 3 years.

Asphyxia, cerebral birth injury, meningitis, systemic infections, kernikterus, congenital malformations and metabolic disturbances such as tetany are among causes of neonatal convulsions given in the majority of reviews. In a study of 176 babies aged less than 4 weeks, Peterman (1946) considered that convulsions were accounted for by birth injury in 69%, acute infection in 10%, develop-

mental anomalies in 4% and tetany in 3%. The present series includes examples of all these conditions together with instances of convulsions associated with exsanguination, intrapulmonary haemorrhage and cold injury. Clifford (1939), Ford (1952), Stone (1945) and McQuarrie and Baird (1959) consider that haemorrhagic disease contributes to a proportion of cases of intracranial haemorrhage. Findings in this study confirm the views of other workers that this is not a frequent occurrence (Craig, 1938; Potter, 1945; Sanford, Shmigelsky and Chapin, 1942). Kagan (1959) makes specific mention of gastro-enteritis. This is contrary to my experience. In a detailed review of 53 cases of acute enteritis in the newly-born in both epidemic and sporadic form no instance of convulsions was encountered.

Recent literature does not refer to alimentary disturbances other than gastro-enteritis as a cause of convulsions in infancy. Thomson (1921), Still (1927) and Hutchison (1931), however, all mention the occurrence of convulsions as a result of the retention of undigested food in the bowel or stomach. They ascribe the convulsions to reflex irritation. Today this explanation is considered inadequate. Nevertheless, in the absence of a convincing alternative and in the absence of evidence of metabolic disturbance the explanation merits consideration in connexion with the few babies in the present series in whom isolated convulsions coincided with the evacuation of undigested stools.

Febrile convulsions are described by Green and Richmond (1954) and McQuarrie and Baird (1959) as especially common in the first two years of life. Davidson (1953) stressing their occurrence in infants considers that of convulsions in all children 2·5% are regarded as 'so-called febrile convulsions'. According to Friderichsen and Melchior (1954) febrile convulsions are rarely seen under the age of 6 months. The youngest patient in 256 children with simple febrile convulsions reported by Livingston (1958) was aged 2 months. Discussing febrile convulsions in general, McQuarrie and Baird (1959) refer to the onset of extracranial infections and to a high environmental temperature as possible contributory factors. An outstanding feature of the series under discussion is the absence of any baby with convulsions which could reasonably be termed febrile in the strict sense of the term. In the few babies with severe urinary infection in whom convulsions occurred the temperatures were subject to fluctuation and were elevated on occasions to 102°-103° F. Pyrexia of the same degree was a feature of the considerably more numerous cases of pyuria lacking any convulsive tendency. Among

infants with meningitis and septicaemia a normal or slightly subnormal temperature was as frequent a finding as an elevated temperature. Pyrexia when present was usually slight. There was no obvious connexion between body temperature and the occurrence of convulsions in these cases. Experience gained in the course of the present study warrants the view that febrile convulsions if they do take place in the first 10 days of life do so with the utmost rarity. There is support for this opinion in the fact that dehydration fever is not accompanied by convulsions. Moreover, over a period of many years I have seen and made records of five newly-born babies with extreme hyperpyrexia attributable to faulty nursing technique or defective incubator control. The rectal temperature ranged from 106° to 108° F. and in each case hyperpyrexia was present for not less than six hours. All the babies recovered without sequelae. None had convulsions. Unfortunately records were not made concerning the rapidity with which the temperatures rose, an aspect of febrile convulsions considered to be important by Wegman (1939).

Severe, extensive cerebral oedema was the sole finding at autopsy in five cases. It was also found in less severe degree in association with other forms of intracranial pathology in three babies born prematurely and in two born at term. The clinical simulation of intracranial haemorrhage by babies with cerebral oedema is noted by Hughes (1952), and McQuarrie and Baird (1959) include acute cerebral oedema among the causes of convulsions in infancy. Judging by the incidence of cerebral oedema among fatal cases in the present series it is possible, indeed probable, that cerebral oedema may account for a considerable number of convulsions in surviving newly-born babies. Certainly cerebral oedema provides one possible explanation for the convulsions occurring in two of the surviving examples of cold injury.

Hypothermia is characteristic of cold injury and was a feature of the two cases in this series. It was a feature also of several of the premature babies dying of infection, and of several infants dying as a result of intracranial haemorrhage. Furthermore, among large babies surviving neonatal cerebral disturbance, convulsions occurred in a number within 36 hours of birth while the body temperature was still below 96° F. There were several examples of twitching movements occurring simultaneously with a sudden drop in body temperature on the third and fourth days of life in particularly small premature babies who eventually survived. These observations do not warrant any conclusions but suggest that a closer relationship may exist between

convulsions in the first few days of life and hypothermia than between convulsions and hyperpyrexia.

Bound, Butler and Spector (1956) in their study of perinatal mortality refer to the occurrence of convulsions in 20, and of cerebral irritation without convulsions in six premature babies dying as a result of the cardio-respiratory syndrome. Their experience contrasts with that at the Leeds Maternity Hospital where over a number of years continuous detailed clinical observations have been made on all infants in whom there was a possibility that signs of the cardio-respiratory syndrome might develop.

During the period in question 38 babies dying with clinical and pathological evidence of the syndrome were observed from the time of delivery in the labour ward until death, with as one particular object the recognition of any convulsive tendencies. All the babies were premature and delivered by caesarean section. Entirely contrary to expectations no convulsions were seen in any of the infants. Insofar as a limited number of cases permits of tentative deductions it seems that the anoxia occurring in fatal cases of the cardio-respiratory syndrome does not of itself give rise to convulsions. A further point is that these cases are not associated with the generalized tonicity and apnoea sometimes seen in very small premature babies. It is of interest in this connexion that McKay and Smith (1959) do not include convulsions among the clinical manifestations of hyaline disease.

'The causes of convulsions (in infants) are legion.' This statement of Still's (1927) can be applied with justification to the newly born. It is important, however, that the occurrence of convulsions in the early days of life should be seen in proper perspective. Although the causes are legion the analysis in Table 8 indicates that no one clinico-pathological condition is invariably associated with convulsions. The highest incidence was found in babies with cerebral agenesis. Of the 21 babies, no fewer than 17 had major convulsions. The clinical pattern in these was unlike that associated with other forms of intracranial pathology, and it is considered that it has a diagnostic significance. Particular attention should be paid in this connexion to major convulsions commencing within a day or two of life, persisting at irregular intervals despite heavy anticonvulsant therapy, and occurring in an infant with asymmetrical anomalies of the face or cranium.

There was a high incidence of convulsions among babies with septicaemia and meningitis. Convulsions cannot, however, be regarded as fundamental to diagnosis. They were absent in a number of babies with widely dispersed septicaemic foci and

thick inflammatory exudate covering the entire surface of the brain. Clinical features requiring the exclusion of infection as a cause of convulsions include the presence simultaneously of an unexplained low body temperature, grey cyanosis and reluctance to feed. A leucocytosis or leucopenia is in favour of infection whereas a normal white cell count is not.

This study makes it abundantly clear how rarely a precise diagnosis is possible during life. Convulsions in the presence of unconsciousness and of deepening cyanosis not responding to oxygen therapy suggest pressure on the mid-brain or brain stem by haemorrhage arising from a dural tear. An uncontrollable encephalopathic picture punctuated by convulsive seizures following difficult delivery of a large or post-mature infant is suggestive of intracerebral and/or intracerebellar multiple perivascular haemorrhages. The dramatically sudden appearance in a premature baby of violent, generalized convulsions, a bulging fontanelle and an agonizingly piercing cry is in keeping with intraventricular haemorrhage. Otherwise there is no clinical picture (apart from that already described in connexion with cerebral agenesis) characteristic of intracranial pathology of a particular kind or with a particular anatomical location.

Terminal convulsions irrespective of their pathological explanation and of the maturity of the infant tend to be violent and general. In other circumstances convulsions encountered in small premature babies are generally of a subdued character. Mention has been made of the occasional simultaneous occurrence in these babies of transient cyanotic apnoea and generalized tonicity. Incidents of this kind can occur as completely isolated events or as events interspersed between phases of subdued twitching or myoclonic activity. As Green and Richmond (1954) point out, young infants may demonstrate only the tonic phase of a major convulsion. There were occasions when even momentary apnoeic attacks might in reality have been minimal convulsive incidents, but they were not regarded as such for the purposes of this study. Nevertheless, the extent to which the frailty of prematurity tends to subdue the severe manifestations of convulsive tendencies was very evident. For this reason it is considered that assessment of the potential risks of convulsions in the early days of life must have regard to the maturity and physical robustness or otherwise of the baby.

Observations made in the present study do not agree with the conclusion of Keith, Norval and Hunt (1953) that 'difficulties during delivery have very little to do with persistent neurological abnor-

malities' in surviving infants, and do not support the view advanced by Hellström and Jonsson (1953) that asphyxial attacks appearing 'later on and after the child has breathed normally' have a less favourable prognosis. The findings in the follow-up series (Table 9) do suggest, however, that the general risk of morbid sequelae is as great in the case of premature babies with slight transient convulsions as in babies born at term having prolonged major convulsions.

Summary

The clinical findings in 374 newly-born babies who had convulsions commencing within 10 days of birth are presented.

The pathological findings in 158 fatal cases are considered in relation to clinical observations made during life.

Surviving cases are considered according as the diagnoses were proven or presumptive.

Attention is drawn to the characteristics of convulsions arising in cases of cerebral agenesis.

Emphasis is attached to the absence of 'febrile convulsions' and of convulsions in association with uncomplicated cardio-respiratory syndrome.

The occasional occurrence of convulsions in the presence of cerebral oedema and hypothermia is noted.

The influence of prematurity and the prognostic significance of transient minimal convulsions in premature babies are discussed.

The study was only made possible by the courtesy of senior obstetrical colleagues and by the enthusiastic assistance of a succession of registrar colleagues too numerous for individual mention. I am indebted for assistance to Miss M. Pattullo and Sister R. White in making clinical observations, and to the Librarian, the Royal College of Physicians, Edinburgh, in obtaining references. Especial thanks are due to Dr. Agnes Macgregor, Dr. W. Goldie and Dr. D. G. F. Harriman for their invaluable criticism and advice.

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FAMILIAL DIFFUSE PROGRESSIVE ENCEPHALOPATHY

BY

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The purpose of this paper is to present the clinical and neuropathological findings in two idiot brothers in whom the mode and time of onset and the pattern of brain anomalies were remarkably similar. Clinically there were similarities with well-known syndromes such as Tay Sachs and Schilder's disease. However, the ultimate diagnosis was to emphasize the frequent difficulties encountered in determining the aetiology of mental deficiency with progressive neurological features.

Family History

The parents, each an only child, were English and in good health. There was no history of consanguinity, mental illness, epilepsy, ataxia, blindness, skeletal deformity or other neurological disease in three generations of the family.

Case Histories

Case 1. This child, the first, was born when the father was 29 years old and the mother 28. The mother attended an antenatal clinic and, after seven months gestation, developed hydramnios. Pregnancy was otherwise normal as far as is known and the baby was born at full term. The presentation was occipito-posterior, labour was prolonged, and the child was delivered by forceps. No asphyxia was noted at birth but the child's head was bruised. The birth weight was 9 lb. 3 oz. (4,160 g.). He was regarded as normal until 3 weeks old, when epileptiform movements were noticed on several occasions. At 6 weeks these movements started again. They consisted of a spasmodic twitching of the neck to the right, and of the left arm and leg, and increased in severity to involve the whole body, which became straight and rigid with the head and eyes deviated to the left and the face becoming red. To begin with he had between two and four such attacks a day but this became increasingly more frequent until he was having between seven and 10 or more, despite treatment with phenobarbitone.

Initially, he was breast fed but at 7 weeks increasing difficulty with sucking made it necessary to substitute spoon feeding. Up to this time he had been considered a normal child mentally and physically, apart from the

seizures. From then on he deteriorated and at the age of 3 months he was described as lying helpless and barely able to move his limbs. He never smiled and appeared to be blind. By the age of 3 years and 2 months he was described as inert, silent, helpless and drowsy all day. He was unable to sit up and could move only his right leg slightly. He failed to respond to any stimuli except painful ones which provoked a monotonous scream. He was deaf and speech had not developed. Feeding was difficult because of the extreme slowness in swallowing. He suffered from severe constipation. Mentation and behaviour were such that both were described as 'less than that of a new born child'. He had no grasp reflex and his developmental quotient was zero.

CLINICAL FINDINGS. On admission to the Fountain Hospital he weighed 10.6 kg., height 84.2 cm. (normal for age and sex is 14.61 kg., height 96.7 cm.).

At 3 months old his head was markedly asymmetrical, though its circumference (45.1 cm.) was slightly larger for age (normal: 40.9 cm.). At 3 years 2 months the circumference (49.5 cm.) was still within normal limits (normal: 50.4 cm.), but the asymmetry was more marked. The left frontal region had become very prominent and there was left occipital bossing. His teeth were yellowish. A spastic paralysis was more marked on the left side, especially the leg. There was a right facial weakness, the right palpebral fissure being wider than the left and the movements of the muscles of the forehead and the right side of the mouth being diminished. Contractures of the wrist flexors were present, the hand being flexed at the metacarpophalangeal and extended at the interphalangeal joints. A severe thoracolumbar scoliosis and talipes equino-varus was observed. Babinski's sign was positive on both sides and the knee and other tendon jerks were exaggerated while the abdominal reflexes were absent. A light bilateral rotary nystagmus was also noted. The optic discs were atrophic, the edges being clear cut. Vessels of the fundi and the maculae were normal.

On the ninth day after admission to the Fountain Hospital he developed bronchopneumonia. He died 16 days later, at the age of 3 years and 2 months.

INVESTIGATIONS. C.S.F. examinations showed no abnormality and W.R. and Kahn tests were negative. An air encephalogram revealed internal hydrocephalus.

PATHOLOGICAL FINDINGS. The necropsy, on the day

after death, was done by the Coroner's pathologist. The cause of death was acute suppurative bronchopneumonia.

The fixed brain, asymmetrical due to the right hemisphere being slightly larger than the left, with the cerebellum and brain stem, weighed 915 g. (average normal for age is 1,141 g.). Radiographically, the ventricles were moderately distended; there was no evidence of calcification. The meninges over the frontal lobes and tips of the temporal lobes were opaque and congested. The superior and middle frontal, and the superior precentral sulci, were widened. The surface of the uncus was finely granular; the entire corpus callosum was very thin, being only 1 mm. thick in its thinnest part. The basal ganglia looked normal. There were widespread fine ependymal granulations of the lateral ventricular walls. The optic nerves were small and at the chiasma were 2.5×1.5 mm. (normal 4.7 mm. (Duke-Elder, 1932)), but other cranial nerves and the vessels at the base of the brain were normal.

HISTOLOGICAL FINDINGS. Coronal sections of the frontal, parietal and occipital lobes, the basal ganglia with temporal lobes, the mid brain, pons, medulla and cerebellum were embedded in celloidin and sections stained by the usual neuropathological procedures—Nissl, Heidenhain, H.V.G., Mallory's P.T.A.H. and Holzer. Paraffin and frozen sections were used when necessary for the Holzer, Kultschitzky-Pal, Bielchowsky, Turnbull and Scarlet R methods.

There were conspicuous structural changes in the cerebral hemispheres. Nerve cells were sparse in all

regions of the cortex, being most marked in layer III. Surviving cells appeared normal in size and shape. Status spongiosus affected some cortical areas at the level of layer III. Perigyril gliosis was marked in the frontal, parietal and occipital lobes and to a much less extent around the uncus. Apart from shallow undulations of the surface of the uncus and this slight gliosis, there was no histological explanation such as granular atrophy to account for the curious naked eye granular appearances of the part.

The white matter in the parietal, temporal and occipital lobes was abnormally pale in sections stained by myelin techniques. Higher magnifications revealed various stages of degeneration of the myelin sheaths and breakdown such as tortuosity, focal ballooning, varicosity, uneven staining and beading. Astrocytes were increased throughout the white matter and there was a fine reticular fibrous gliosis in the corona radiata and the central core of white matter of the gyri of the frontal, parietal, temporal and occipital regions; it was densest in the tapetum. Lipid phagocytes were confined locally in a scanty fashion to the vicinity of blood vessels. There were no areas of localized softenings, tissue breakdown and cyst formation in the white matter. The arcuate fibres were involved to an equal extent with other white fibre tracts.

The thalamus, striatum and pallidum appeared to have a normal number of healthy looking cells and a normal amount of white matter. Fibrous gliosis was absent. Similarly the corpus Luysii and red nucleus were healthy.

Comparison of the mid brain section at the level of the superior corpora quadrigemina with a similar section



FIG. 1a.—Case 1, paucity of cells in the substantia nigra of one half of the mid-brain. H.V.G. $\times 6$.



FIG. 1b.—Case 2, absence of cells in the substantia nigra. H.V.G. $\times 6$.

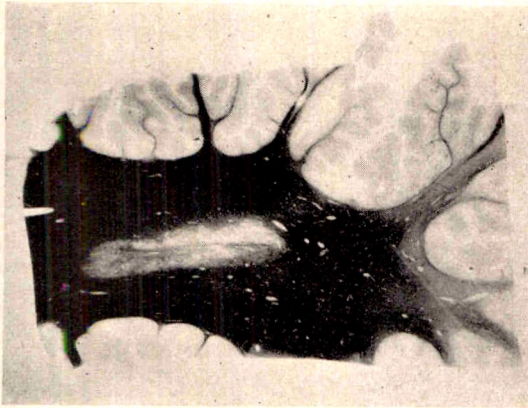


FIG. 2.



FIG. 3.

FIG. 2.—Case 1, pallor of the cerebellar white matter. Kultschitzky-Pal $\times 2\frac{1}{2}$.

FIG. 3.—Case 1, gliosis of the cerebellar white matter. Holzer $\times 2\frac{1}{2}$.

FIG. 4.—Case 1, foci of perpendicular gliosis in the molecular, Purkinje cell and granular cell layer caused puckering of the surface of the folia. Mallory's P.T.A.H. $\times 100$.

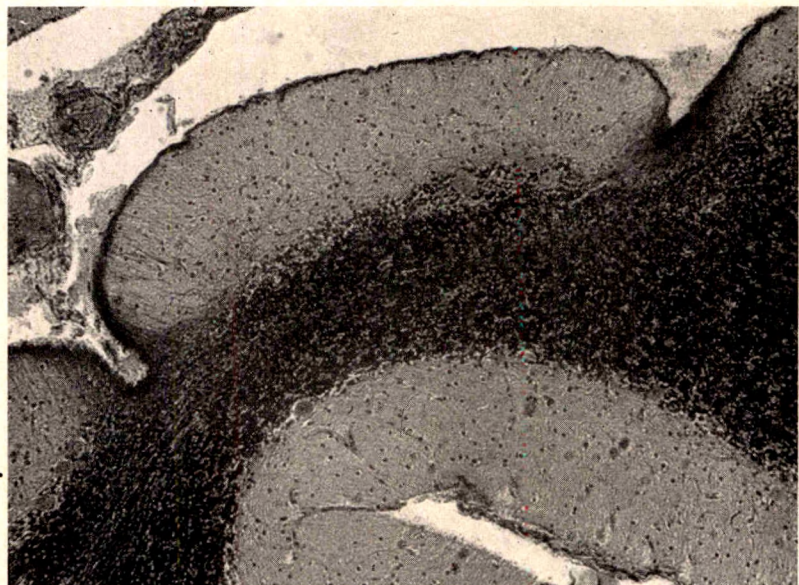


FIG. 4.

from a control brain (a child aged 18 months) revealed definite sparseness of nerve cells in the substantia nigra. Those cells present lacked pigment, a normal finding at this age, and were in three or four scattered groups (Fig. 1a). Status spongiosus affected the area. In other parts of the brain stem there was a normal complement of healthy looking cells in the olives pontine and cranial nerve nuclei. The pyramids were small and pale. Fibrous gliosis was present in the inferior olives and in their central core of white matter, hila and white fibres around their convolutions. A fine diffuse network of glial fibres was present throughout the reticular formation.

Periventricular gliosis was increased around the dilated ventricles. The ependyma was absent in places and replaced by ependymal granulations—a feature most marked in the fourth ventricle.

Cellular components of the cerebellum were fewer in numbers than normal. This was most obvious in the dentate nucleus but Purkinje and granular cells were also reduced in numbers. Pallor of the myelin was present in the central core of white matter of the dentate nucleus, and medullary white matter of the cerebellum and the central core of the folia and leaflets (Fig. 2). There were large globules up to 70 μ in diameter around several blood vessels which stained with the myelin stain. All parts of the cerebellum exhibited fibrous gliosis with an increase of glial cells; for instance, there were reticulated masses of fibres in the medullary white matter and folia (Fig. 3), and in the molecular, Purkinje and granular cell layers there were focal areas of perpendicular gliosis (Fig. 4).

The optic nerves were demyelinated and composed of a network of glial fibres surrounding lacunae from which the myelin sheaths had disappeared.

Pia arachnoid vessels were congested. A fine picrophilic deposit was present under the pia in places. The pia arachnoid was thickened and fibrosed over the frontal region, but in other cases the membranes were normal.

Clear lacunae were present around many blood vessels, especially those in the grey matter and brain stem. In several instances similar spaces were filled by a fine picrophilic substance.

There was no evidence of lipoidosis, abnormal pigmentation or calcification.

Case 2.—Pregnancy was apparently normal, the child being delivered by caesarean section just before labour began. This operation was performed at the mother's request to avoid a possible birth injury—to which the elder brother's condition had been attributed. The birth weight was 8 lb. 15 oz. (4,040 g.). Discharge from the hospital was on the 21st day, normal progress apparently having occurred. At 7 weeks, he was admitted to hospital because he had started having epileptic seizures. They were tonic in type beginning with sudden jerks of the limbs after which the whole body stiffened. The face became cyanosed and frothing of the mouth occurred. These seizures persisted with increasing frequency and were triggered off by the slightest stimuli, especially during feeds. As in his brother, phenobarbitone seemed to have no effect on the course of the fits. Feeding difficulties were also present, and he suffered from severe constipation.

He was regarded as a normal baby up to 7 weeks old when the fits started. After that mental deficiency gradually became more and more obvious and by the time he was admitted to the Fountain Hospital at 15 months, he was a gross idiot. He lay inert in bed, in a sleep-like state most of the time. He appeared to be blind and was probably deaf, though he was thought to respond to the sound of a bell by momentarily widening his eyes and blinking. He failed to respond to any stimuli except painful ones to which he reacted by crying in a faint monotone. He was unable to suck, having to be fed slowly with a spoon; he had no grasp reflex and his developmental quotient was scored as less than one month, i.e. a little better than that of the elder brother.

CLINICAL FINDINGS. On admission to the Fountain Hospital he weighed 10 kg., height 75 cm. (normal for age and sex is 10.75 kg. and height 78.5 cm.). The head circumference was 45.6 cm. (normal for age and sex is 48 cm.).

At 7 weeks his head was noticed to be asymmetrical. The right side of the skull had a steeper contour than the left and the anterior fontanelle had closed by 15 months. The nose was flat and the eyes were slit-like. No teeth had erupted. His extremities resembled those of a young infant. The thumbs were flexed firmly within the palms of the hands. He was unable to hold up his head, to sit up or perform any other coordinated movements. The muscle tone was slightly increased. The Babinski sign was present bilaterally, though all the tendon jerks and abdominal reflexes were reported

absent. His testicles were undescended (as was the case with the elder brother).

On the eighth day after admission to the Fountain Hospital, he suddenly collapsed with severe dyspnoea, with a high fever and signs of bronchopneumonia. He died two hours later, at the age of 16 months.

INVESTIGATIONS. At 7 weeks skull radiograph was normal. Subdural explorations revealed no haematoma. The optic discs were pale. C.S.F., serum chlorides and W.R. were all normal.

PATHOLOGICAL FINDINGS. The necropsy on the third day after death was performed by the Coroner's pathologist. Death was due to bronchopneumonia.

The fixed brain, asymmetrical due to the right hemisphere being slightly larger than the left, with the cerebellum and brain stem weighed 807 g. (average normal for age is 944 g.). Radiographically, the lateral ventricles were moderately distended; there was no evidence of calcification. The meninges were congested but not opaque. The superior frontal, superior precentral and cingulate sulci were widened. The corpus callosum was thinner than normal throughout its length; its mid part was 1 mm. thick. The surface of the uncus, as in the brother, was finely granular (Fig. 5). The basal



FIG. 5.—Case 2, the granular appearance of the surface of each uncus accentuated by a network of vessels.

ganglia appeared to be normal size. The ependyma was smooth. The optic nerves were small and at their approach to the chiasma were 2.75×2.0 mm. (normal 4 to 7 mm. (Duke-Elder, 1932)). The other cranial

nerves were normal and vessels at the base of the brain were normal.

HISTOLOGICAL FINDINGS. Coronal sections were prepared and stained as for Case 1. The findings in the cerebrum, brain stem, cerebellum and optic nerves were very similar to those of the brother, although there were some differences, notably in the extent of damage in the two cases.

The substantia nigra of Case 2 was more severely affected than Case 1 (Fig. 1b). Nerve cells were almost completely absent and those which remained were degenerated ghost forms. Unlike Case 1, similar changes to those in the substantia nigra were present in the corpus luyisii. There was a condensation of dense glial tissue around the putamen of Case 2 (Fig. 6) in whose brain stem all parts were more gliosed than in the brother. Gliosis was particularly dense in the trapezoid bodies, the grey part of the reticular formation, the XII nerve nucleus, and in and around the inferior olives. Cerebellar involvement was less than in Case 1, for instance, the molecular, Purkinje and granular cell layers had escaped gliosis, although their numbers were reduced. The dentate nucleus and white matter were diseased

curious naked eye appearances of the granularity to the surface of the uncus since perigyril gliosis was much less than in Case 1. The surface was definitely more undulant than usual and the hollows were occupied by congested meningeal vessels, otherwise the architectonics were quite normal.

Discussion

Cases bearing some similarity to these brothers have been described by Alpers (1931) and called 'diffuse progressive degeneration of the grey matter of the cerebrum'; Christensen and Krabbe (1949) who called their case 'poliodystrophia cerebri progressiva (infantis)', and Ford, Livingston and Pryles (1951) who called the condition 'familial degeneration of the cerebral grey matter in childhood'. Wolf and Cowen (1956) included a case under the heading 'diffuse progressive cerebral cortical atrophy'. Their principal findings are listed in the Table.

Convulsions, the earliest clinical manifestations in our cases, commenced at 3 weeks (Case 1) and 7 weeks (Case 2) and were earlier in onset than those of other observers. It was possible that the illness occurred prenatally in Case 1 since hydramnios was associated with intra-uterine life from the seventh month. This accords with a view expressed by Christensen and Krabbe (1949) who thought that the disorganization of the cortical cellular layers in their case was congenital in origin although they could not exclude the possibility that it may have been a consequence of later degeneration.

Ataxia and choreo-athetoid movements present in some of the reported cases (see Table) were absent in the brothers. This was possibly due to the widespread lesions masking the expected clinical features.

Despite the patients' failure to pass any developmental milestones, there were features that the disease was progressive, borne out by the fits becoming more frequent and severe, increasing drowsiness and increasing paralysis of the limbs. This conformed with the findings of Christensen and Krabbe (1949) who found a series of features indicating postnatal progressive processes.

Birth trauma was an unlikely cause of the condition, especially in view of the extra care taken to prevent this in Case 2, and the lack of supporting pathological features such as ulegyria (cortical atrophy) and *état marbré* (marbling) the cause of which is often attributed to birth injury. Slight meningeal thickening and some ependymal granulations in Case 1 suggested an infective cause, but both these features were absent in the other child. Since the lesions in the two brains were so similar in other respects, it was felt that the basic cause of the



FIG. 6.—Case 2, glial tissue around the putamen. Holzer $\times$ 5.

in a similar manner to Case 1. Case 2 had no ependymal granulations, although periventricular gliosis was increased. The meninges were nowhere thickened. There was apparently less histological evidence to explain the

TABLE
COMPARISON OF CASES
DISEASES TO BE CONSIDERED IN THE DIAGNOSIS OF THE TWO PRESENTED CASES

Authors	No. of Cases Reported	Age at Onset	Clinical Features	Neuropathological Findings
Alpers, 1931 Diffuse progressive degeneration of the grey matter of the cerebrum	1	3 months	Convulsions, hyperkinesis, generalized rigidity, increased tendon reflexes, unable to hold up her head, died at 5 months	Defective cortical development, neuronal degeneration and astrocytic proliferation in cortex, striatum, pallidum and thalamus, cerebellum spared
Christensen and Krabbe, 1949 Poliodystrophy cerebri progressive (infantilis)	1	8 months	Delayed milestones and mental retardation and gradual deterioration of both mental and physical conditions. Increasing spasticity and myoclonic contractions, abnormal tendon reflexes, paresis and ataxia, optic atrophy and probably deaf and dumb, dental anomalies up to four generations, died at 2½ years	Cerebral atrophy with secondary increase in microglia, whereas white matter was fairly well preserved. Similar findings in basal ganglia, cerebellum and brain stem
Ford, Livingston and Pyles, 1951 Familial degeneration of the grey matter in childhood	4	Cases 1 and 2 6 years Case 3 6 months Case 4 4 years	Mental retardation, epileptic fits, myotonic and choreo-athetoid movements, increasing spasticity, hemiplegia and progressive dementia. Cases 1 and 2 were sister and brother and maternal uncle died in status epilepticus	Cortical atrophy, destruction of neurones, proliferation of astrocytes, microglia and capillary proliferation and secondary myelin loss. Thalamus, corpus subthalamicum and substantia nigra, striatum, cerebellar cortex and dentate nuclei were degenerated
Wolf and Cowen, 1956 Diffuse progressive cerebral cortical atrophy	8	3 months to 2 years	Epileptic seizures, spasticity, mental retardation, blindness and spastic quadriplegia	Cerebral atrophy with loss of nerve cells; thalamus, cerebellum, corpus striatum, caudate and dentate nuclei and putamen affected (Some degeneration of posterior-column and spino-cerebellar tracts in spinal cord in one case)
Presented cases	2	At birth	Fits, blindness, hypertonus, nystagmus. Babinski response variable, idiocy early in onset	Paucity of nerve cells in cortical grey matter, cerebellum and substantia nigra. Pallor of myelin corona radiata and cerebellum. Fibrous gliosis around inferior olivary nuclei, in tegmentum and in Case 2 around lentiform nucleus. Optic nerves pale and gliosed.

lesions had some other origin with perhaps secondary infection complicating Case 1; however, this was not proved during life by clinical investigations.

Two of the cases described by Ford *et al.* (1951) were half-sibs (brother and sister). Malamud and Cowen (1958) described findings in two male first cousins which they regarded as an unusual form of cerebellar ataxia transmitted by sex linked inheritance. Only one case was examined pathologically and features similar to some of those of the brothers were described, for instance, gliosis of the cerebellar folia, dentate nucleus, inferior olives, basal ganglia and optic tracts.

An appraisal of the clinical and pathological evidence and that of the reported cases suggested that the lesions in these brothers were probably determined prenatally. It was felt that genetic factors may be an important influence; though there was no proof of this, however, it would concur with our view from experience that there may be several forms of mental deficiency other than well-known conditions such as phenylketonuria, amaurotic idiocy and so forth, which may be caused by genetic factors.

'Degeneration of the cerebral grey matter', part of the descriptive name used by Alpers (1931), Christensen and Krabbe (1949), Ford *et al.* (1951) and Wolf and Cowen (1956) was too limiting in view of the changes in the cerebral white matter, the brain stem and cerebellum, and it seemed more appropriate, if the disease is the same, to call the condition familial diffuse progressive encephalopathy in childhood.

Summary

A disorder involving a diffuse progressive encephalopathy occurred in two brothers, beginning in the first possibly before birth and in the second around the time of birth.

A family study failed to reveal similar cases.

The main clinical features consisted of progressive mental deterioration, epileptic fits and increasing spasticity and paralysis. Both children became deaf and blind. Apart from slight nystagmus, there were no involuntary movements or other signs of a cerebellar disorder. Kyphoscoliosis and equinovarus were present in both.

The principal neuropathological features were paucity of nerve cells in cortical grey matter, cerebellum and substantia nigra. There was pallor of myelin in the corona radiata and the cerebellum. Fibrous gliosis was present around the inferior olivary nuclei, in the tegmentum and in one case around the lentiform nucleus. The optic nerves were pale and gliosed.

Norms of weight, height and head circumference are quoted from *Studies of Child Health and Development*, Harvard School of Public Health, in Nelson's 'Textbook of Pediatrics', Philadelphia, 1959.

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POSTNATAL PLASMA SHIFT IN PREMATURE INFANTS

BY

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In the normal infant birth is usually followed by a substantial rise in the concentration of haemoglobin (Hb) and in the packed cell volume (PCV) of the blood, while the concentration of plasma protein tends to rise only slightly (Gairdner, Marks, Roscoe and Brettell, 1958). From these facts we have inferred that immediately following birth there is a loss from the vascular compartment of a large fraction, up to a quarter or more, of the circulating plasma.

We do not know the fate of the plasma lost from the vascular compartment, but we have suggested that the major changes which take place in the pulmonary circulation at birth might be expected to favour a shift of fluid from the circulation at this site. If so, then shift of plasma into the interstitial spaces of the lung might play a part in the pulmonary failure which so often overtakes the premature infant in the first few hours or days after birth. For this reason, we have extended our observations to premature infants to determine whether there is any relationship between the postnatal haemoconcentration effect and the development of pulmonary symptoms.

Material and Methods

Cord blood was obtained from 24 infants with birth weight of less than 2,500 g., of whom 22 were born vaginally and two by caesarean section. Maternal toxæmia was present in six cases. Neither the method of delivery, nor the presence of maternal toxæmia appeared to affect the results, and they have not been separately analysed here.

The cord was always clamped as soon as conveniently possible, both in vaginal and in caesarean deliveries. A blood sample was taken by puncture of the umbilical vein between placenta and clamp. Subsequent specimens were taken by insertion of a polyvinyl cannula (internal diameter 1.0 mm.) into the umbilical vein, or in a few cases by femoral vein puncture. Samples were taken into siliconized bottles containing ethylenediamine tetra-acetate as anticoagulant.

Hb concentration and PCV were estimated as described previously (Marks, Gairdner and Roscoe, 1955), in duplicate in most cases. Plasma protein

concentration was estimated by the biuret method using 0.2 ml. plasma. The estimations required less than 2 ml. blood.

The infants were closely observed for signs of respiratory distress; those commonly observed were rapid moaning respirations, often with rib recession. Nine infants showed such signs and six of these recovered.

Three infants died at 20, 22 and 32 hours; all showed respiratory distress by five hours or earlier. At necropsy the lungs showed the picture of secondary atelectasis with hyaline membrane in all three cases, together with massive intra-alveolar haemorrhage in one case, and broncho-pneumonia in another.

Results

Change in Hb Concentration a Few Hours after Birth. A second specimen of blood was obtained from 24 premature infants at some time between one and eight hours after birth, in most instances about two hours after birth. The mean Hb was 17.9 g./100 ml. (S.D. 2.0) in cord blood and 19.4 g./100 ml. (S.D. 2.3) at one to eight hours. The difference of 1.5 g./100 ml. is just significant ($P=0.05$).

Fig. 1 shows the change in the Hb concentration shortly after birth related to the initial cord Hb.

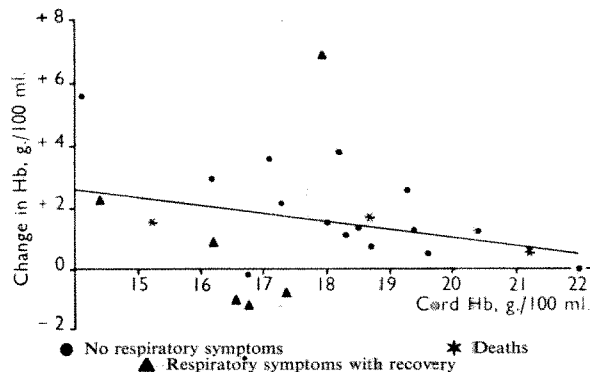


FIG. 1.—Relation of change in Hb level 1–8 hours after birth to initial (cord) Hb level, in 24 premature infants, of whom nine showed respiratory distress symptoms with three deaths. A regression line has been drawn, but the correlation coefficient is not significant.

There is some tendency for the change to be larger when the cord Hb level lies towards the lower side of normal, but the correlation is not significant (correlation coefficient -0.23).

The degree of postnatal haemoconcentration observed in the nine infants who subsequently developed respiratory distress, including the three who died, was similar to that in the remainder of the group.

Change in Mean Corpuscular Hb Concentration (MCHC) a Few Hours after Birth. Hb and PCV were estimated in cord blood and again in a second specimen taken between one and eight hours after birth, and Fig. 2 shows the percentage change in PCV compared with the percentage change in Hb concentration. Had the Hb concentration and

Change in Plasma Protein Concentration a Few Hours after Birth. Plasma protein concentration could not be measured in all cases, because findings were often invalidated by haemolysis, even a trace of which renders inaccurate measurements of plasma protein. We have not discovered means of avoiding this annoying tendency for blood samples taken in the early neonatal period to undergo haemolysis.

In the nine cases where full data were available, no consistent change in plasma protein concentration was found. The mean concentration in cord blood was 5.3 g. and between one and eight hours 5.2 g./100 ml. Four subjects showed decreases of up to 9%, one showed no change and four showed increases of up to 12%.

Discussion

The Postnatal Haemoconcentration Effect and its Relation to Pulmonary Failure in Premature Infants. Comparing the Hb concentration in blood at birth (cord blood) with that after birth (1-8 hours), our findings in premature infants show essentially the same changes in haemoconcentration as were previously found in normal infants (see Table).

TABLE
POSTNATAL CHANGES IN BLOOD IN NORMAL AND PREMATURE INFANTS

		No. of Cases	Cord Blood	At 1-8 Hours	Postnatal Change %
Normal	Hb, g. %	92	16.6	19.1	+16
	MCHC, %	92	32.3	33.6	+4
	Plasma protein, %	17	6.5	7.0	+8
Premature	Hb, g. %	24	17.9	19.4	+9
	MCHC, %	24	32.3	33.3	+3
	Plasma protein, %	9	5.3	5.2	-2

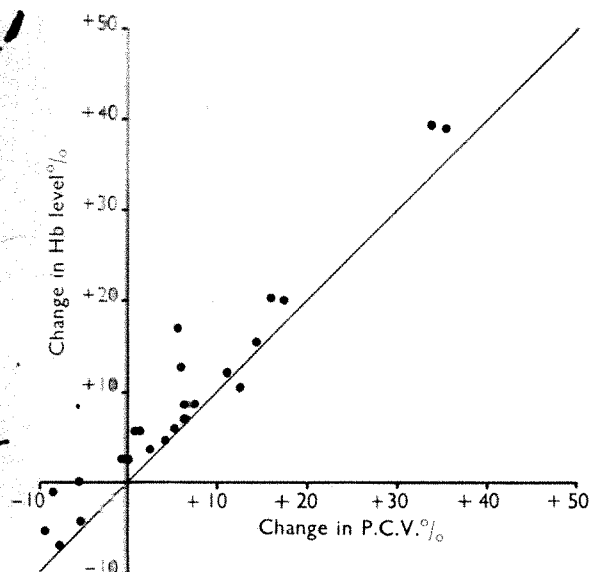


FIG. 2.—Relation of change in Hb level 1-8 hours after birth to change in packed cell volume, 24 cases. The line bisects the axes. Note that the change in Hb exceeds the change in PCV.

PCV moved strictly in parallel, the points would have been grouped about the straight line bisecting the axes. In fact, all but one point fall above this line showing that the rise in Hb concentration is proportionately greater than the rise in PCV. Since the ratio $\frac{\text{Hb concentration}}{\text{PCV}}$ defines the mean corpuscular Hb concentration (MCHC), these results indicate a postnatal rise in MCHC.

The mean MCHC of cord blood in the 24 cases was 32.3% and in blood at one to eight hours, 33.3%, a postnatal rise of 3%.

In our earlier paper we considered in turn the possible causes of the postnatal rise in Hb concentration as seen in normal infants, and arrived at the conclusion that it results from a reduction in plasma volume (Gairdner *et al.*, 1958). The same arguments and the same conclusion must apply equally to the present findings in premature infants.

The fact that while the concentration of Hb in the premature rises by an average of 9%, the concentration of plasma protein remains virtually unchanged, implies that the fluid leaving the vascular compartment contains about the same concentration of protein as does plasma. Thus we conclude that in premature infants as in normal infants, birth is often immediately followed by the loss of an appreciable fraction of the plasma from the vascular compartment.

As an instance of the magnitude the plasma shift may attain, details of one case are given. A 35-week

premature infant with a birth weight of 2,240 g. had a cord blood Hb level of 18.1 g./100 ml. and a PCV of 56%. At 8 hours the Hb level had risen to 25.2 g. and the PCV to 75%. It was formerly shown (Gairdner *et al.*, 1958) that the ratio

$$\frac{\text{Plasma volume at birth}}{\text{Plasma volume after birth}}$$

is given by

$$\frac{\text{Hb}_2 (1 - 0.83 \text{ PCV}_1)}{\text{Hb}_1 (1 - 0.83 \text{ PCV}_2)}$$

where the Hb level and the PCV are Hb₁, PCV₁ at birth and Hb₂, PCV₂ after birth. Inserting in this expression the values in our case, the ratio

$$\frac{\text{Plasma volume at birth}}{\text{Plasma volume after birth}} = \frac{1.98}{1}$$

so that in this infant the plasma volume after birth was reduced by almost 50%.

In this series the magnitude of the postnatal plasma shift bears no relation to the development of respiratory distress (Fig. 1), so that the present study has provided no supporting evidence for the suggestion that plasma shift, if taking place mainly in the lungs, might cause pulmonary oedema and so lead to respiratory symptoms.

The postnatal rise of 3% in the MCHC is close to the figure found for normal infants, and implies that birth is followed by a shift of fluid from the red

cells. The possible causes of this effect also have been discussed in our earlier paper.

Summary

In premature infants, as in normal infants, birth is frequently followed by a rapid rise in the Hb concentration, and in the packed cell volume of venous blood, while the mean corpuscular Hb concentration of the red cells increases.

The cause of these changes is considered to be a considerable loss of plasma from the vascular compartment, and a small shift of fluid from the red cells.

The site at which the plasma leaves the vascular compartment remains undecided. It was suggested that the shift might take place particularly from the pulmonary circulation and so contribute to the development of pulmonary oedema and respiratory failure in the premature infant, but the development of respiratory distress in the premature infants studied could not be shown to be related to the magnitude of the plasma shift.

One of us (A.C.L.C.) was in receipt of a grant from the Elisabeth Storey Fund.

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ABSORPTION OF RADIOACTIVE IRON BY ANAEMIC INFANTS

BY

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The oral administration of iron to anaemic infants often fails to restore the haemoglobin level as rapidly as it would in an adult. The reason for this failure could be either failure of absorption or failure to utilize the iron which had been absorbed, or deposition of all the iron in the tissue stores without any being incorporated in the haemoglobin. It was therefore decided to study the absorption and utilization of iron in anaemic infants and children using tracer quantities of the isotope ^{59}Fe administered orally.

Method

Three control and six anaemic infants and children were studied. Blood and marrow studies were made in all cases. The anaemic cases had a haemoglobin range of from 3.0 to 9.6 g.

	% of Dose Appearing in Blood	% of Absorbed Iron Appearing in Blood	% of Dose Recovered in Stool	% of Dose Absorbed	Haemoglobin (g.)
Controls					
J.N.	40.0	63.5	37	63	11.0
F.D.	3.7	5.8	37	63	10.8
J.F.	8.7	21.7	60	40	10.8
Anaemic Patients					
W.A.	4.0	40.0	90	10	9.6
I.Mc.L.	31.0	50.0	62	35	8.5
F.C.D.	6.0	40.0	85	15	8.4
J.M.	4.0	11.1	64	36	9.6
M.D.	15.4	16.7	8	92	4.8
P.S.	20.0	23.2	14	86	3.0

Two microcuries of ^{59}Fe were given in 5 ml. of water which contained 100 mg. of ferrous sulphate or 30 mg. of iron. After oral administration of the dose, the faeces were collected for five days, and bulked. They were then homogenized in a mixer and an aliquot was counted in a well-type scintillation counter. Blood samples were taken on four occasions during the next fortnight into a mixture of potassium oxalate and sodium fluoride anticoagulant, and counted in the same apparatus. An aliquot of the dose was diluted and counted as a standard,

so that the percentage of the dose excreted in the faeces and circulating in the blood stream could be calculated.

Blood volumes were determined in each case by the Evans blue technique (Muldowney, 1957). The highest figure obtained from the blood was added to that from the faeces, and the remaining percentage of the original dose was considered to have entered the tissue stores. In view of the difficulty of performing external body counting tests upon small infants this estimation was not attempted (Wetherley-Mein, Hutt, Langmead and Hill, 1956).

Results

The relation of four factors was studied, the degree of anaemia, the level of ^{59}Fe in the blood, its absorption and its utilization.

Blood Levels of ^{59}Fe . Radioactivity was present in the blood in the first examinations (Fig. 1), on

% in Blood v. Days after Administration

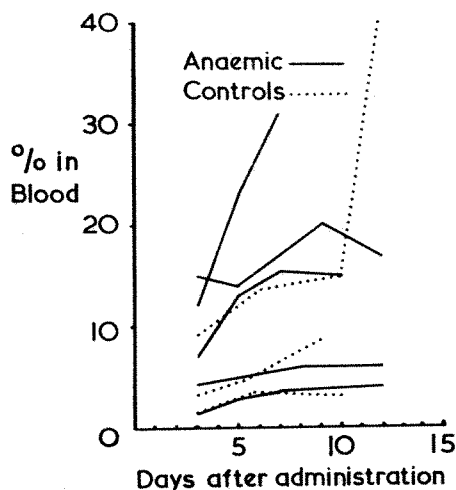


FIG. 1—Showing rise in the percentage of the isotope administered appearing in blood up to a fortnight after administration.

the third day and usually continued to rise steadily until the seventh day. This indicates that oral radioactive iron in tracer doses is rapidly incorporated in haemoglobin. This is in agreement with the findings of other workers.

Effect of Anaemia. The final level reached is directly related to the degree of anaemia present (Fig. 2) and the more severe the anaemia the higher the final level of the isotope in the blood.

Preliminary experiments were conducted using the blood level as a guide to absorption, but it now became apparent, as it had to other workers (Josephs, 1958) that blood levels are reliable as a measure of absorption only if utilization is complete, and this only occurs in the anaemias which follow haemorrhage and in the iron deficiencies of adults. Faecal excretion was therefore also estimated to give an iron balance (Dubach, Callender and Moore, 1948).

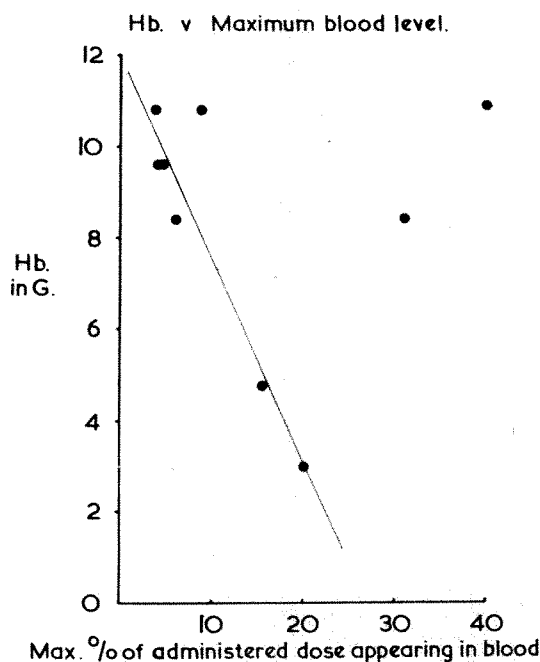


FIG. 2.—Showing that the highest percentages of administered isotope detected in the blood were usually associated with the lowest haemoglobin levels.

Absorption. This was measured from the faecal excretion which was 37-60% of the dose administered in the controls, and 8-85% in the anaemic cases. The remainder of the dose administered which was not recovered in the faeces, was assumed

to have been absorbed. This gave absorptions in the controls of 40-63% with a mean of 49%, and in the anaemic cases of 10-92% with a mean of 45%. These wide variations are in accord with the findings in the literature, where absorptions in controls vary from 1.5-6.5% to 17.69% (Peterson and Ettinger, 1953; Bothwell, Mallett, Oliver and Smith, 1955, quoted from a table by Josephs, 1958).

Inspection of the levels in the anaemic cases (Fig. 3) suggests that there may be two types of anaemic child represented, one with a low absorption and one with a high absorption. This is supported by the fact that the two cases with high absorptions also attained high blood levels of the isotope.

The effect of anaemia upon absorption is considered by most workers to produce increased absorption, but in the present series this was only observed in the two cases in which the diet had been deficient, and there was a decrease in the other cases as compared with the controls.

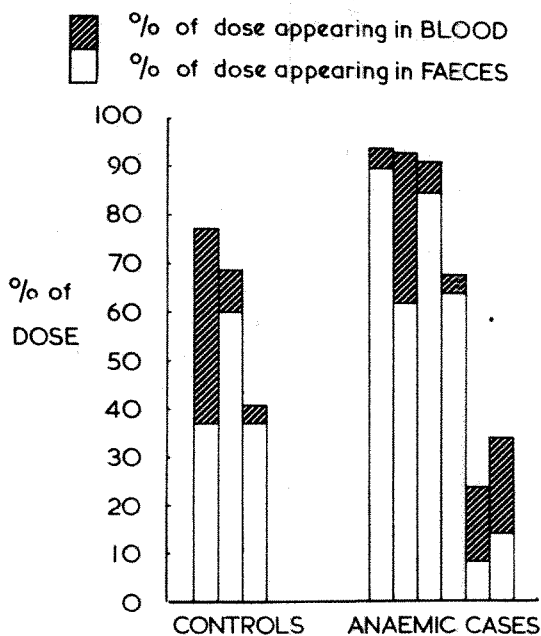


FIG. 3.—Showing the percentages of the isotope recovered from blood and faeces respectively.

Fate of Absorbed Iron. Once iron has been absorbed it may pass either to the tissues or be utilized in haemoglobin formation. Consequently a study of the factors likely to affect this distribution was made.

Level of Isotope in the Blood. There is a direct relationship between this and the utilization of the absorbed iron. The higher the total uptake of ^{59}Fe the higher the percentage utilization of the absorbed iron (Fig. 4).

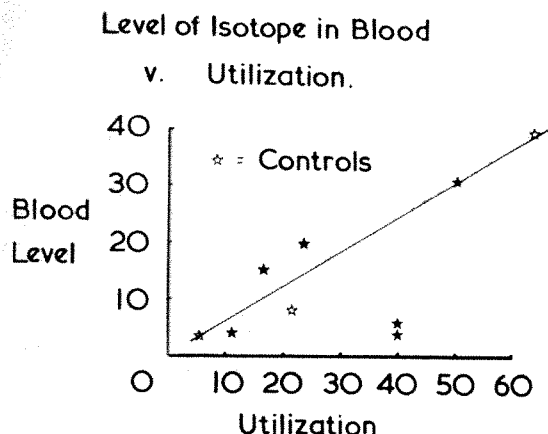


FIG. 4.—The relation between the amount of isotope appearing in the blood and the percentage of the iron absorbed which was utilized for haemoglobin formation.

Anaemia. This did not appear to affect directly the percentage utilization of absorbed iron.

Absorption. This on the other hand did show a slight relationship, a greater percentage of the absorbed iron being used for haemoglobin when the total absorption was low (Fig. 5).

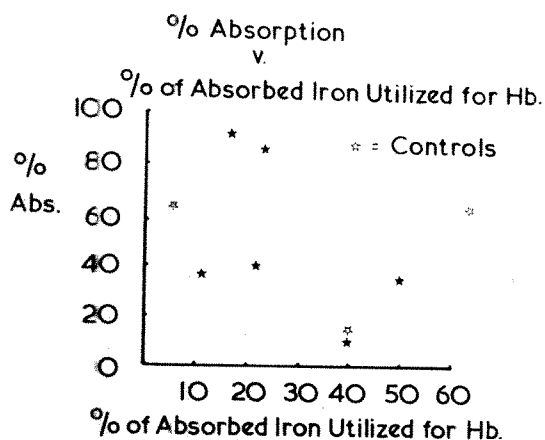


FIG. 5.—Demonstrates the percentage of iron, which, having been absorbed, is used for haemoglobin formation in relation to the total absorption of iron.

In assessing these results it is seen that radioactive iron enters the haemoglobin rapidly and rises to a steady level in about a week. The level ultimately attained, and the percentage of absorbed iron utilized, appear to depend upon the degree of anaemia rather than upon the total amount of iron absorbed. This is also suggested by the slightly higher utilization which occurs in cases of low absorption.

In the two types of anaemia which we have postulated in children, the high absorption and also the anaemia of one type, are both probably the result of depleted body iron stores, while in the other, the stores are probably normal, and the anaemia due in part to impaired absorption.

Discussion

The first investigations of anaemia in infancy showed that the blood picture was similar to that of iron deficiency anaemia in adults. This was the finding in all the anaemic cases of the present series who had hypochromia and microcytosis with the haemoglobin falling much lower than the red cells. Early studies of the effect of giving oral iron to these patients did not show as good results as were obtained in adults. There were in consequence many iron balance experiments performed (McCance and Widdowson, 1938; Hutchison, 1937) all of which showed that much more iron was absorbed than appeared in the red cells and that very little iron was excreted. It was deduced from this that large doses of iron were required for therapy. Studies of the plasma iron made about this time showed that it existed separately from the haemoglobin iron, and that it rose rapidly after ingestion of iron (Moore, Arrowsmith, Welch and Minnich, 1939).

Radioactive iron (Hahn, Bale, Ross, Balfour and Whipple, 1943) was given in tracer doses to dogs and was shown to be absorbed rapidly. This appeared to conflict with the results of the balance experiments but it is now thought that balance experiments conducted over a long period are not strictly comparable with those which study the effects of a single tracer dose. Clinical use of this method demonstrated that anaemic adults had higher absorptions than normal persons (Dubach *et al.*, 1948). The appearance of tracer doses in the blood was the method which was employed in the preliminary experiments of the present series but it became apparent that this was a measure of iron absorption, only if all the iron was utilized for blood production, and this was manifestly not the case (Jeffrey, Freundlich, Jackson and Watson, 1955). It has been shown in adults that this only occurs

after haemorrhage and in iron deficiency anaemia (Josephs, 1958). Balance experiments, in which the faeces were also estimated, were then introduced, and this was the method which we decided to employ. The uptake of intravenous doses of ^{59}Fe has also been studied by some workers (Dubach, Moore and Minnich, 1946) and is found to be increased if the iron stores are deficient, but the method would be difficult to use in children, and the placing of counters over the viscera would be inconvenient in infants.

Studies in children show that absorption is more complete than in adults (Darby, Hahn, Kaser, Steinkamp, Densen and Cook, 1947) and that it is more complete at 7 years than at 9 years. Contrary to former beliefs, absorption does occur at birth, but it may well be that utilization is slower (Oettinger, Mills and Hahn, 1954). Coeliac disease is associated with much impairment of absorption (Badenoch and Callender, 1954). We found this increase in absorption in childhood and we also found considerable variation between individual children. This has been found in the same patient on different occasions by some observers (Smith and Mallet, 1957).

Three sources of iron exist for children: the iron stores laid down at birth; the iron in the food; and therapeutic iron. The birth stores can be calculated, and may be deficient in small infants who grow rapidly, and in whom both tissue and haemoglobin iron may be inadequate in total quantity to supply the demands of growth, almost all of which have to be supplied from the iron present at birth (Smith, Rosello, Say and Yeya, 1955; Hahn *et al.*, 1951).

The food iron is probably adequate in artificially fed infants, since Feuillen and Plumier (1952) have shown that iron is acquired from utensils in the process of preparing the feed. Detailed studies of the absorption of food iron by children using ^{59}Fe have been made by Schulz and Smith (1958a) and they have again found greater, but variable, absorption of iron in children. They also studied the absorption of therapeutic iron (Schulz and Smith, 1958b) and found that anaemic children absorbed more than normal children and normal children more than normal adults, who are generally considered to absorb about 10% of the dose given. Their figures are lower than the present series in some instances, but other authors find higher rates. It is suggested that the present figures indicate two different types of anaemia in children, the one associated with a high uptake and the other with a lower figure. The possible sources of anaemia in childhood are: deficient stores at birth, or undue demand upon those stores, or impaired absorption.

It would appear that the production of haemoglobin and the rate of absorption are not closely related. Provided sufficient iron is available haemoglobin formation will occur. The two variables are the amount absorbed, and the retention and release of this iron by the tissues. Tissue store iron appears to be in two forms (Neerhout, Armstrong, Schulz and Smith, 1958), the one available for haemoglobin synthesis and the other not available. What the factor may be which determines availability has not been determined (Smith *et al.*, 1955).

It appears that there may be two types of anaemia in small children, one associated with impaired absorption and slightly impaired utilization but normal tissue stores, and the other with depleted tissue stores which take up iron with great avidity, and utilize it with increased rapidity for haemoglobin synthesis.

Summary

The absorption and utilization of iron in anaemic infants and children was studied using tracer quantities of the isotope ^{59}Fe .

It is suggested as a result of these investigations, that there may be two types of anaemia in children, the one associated with a low absorption and the other with a high absorption.

The chief factor regulating the appearance of radioactive iron in the blood appears to be the degree of anaemia, and the chief factor regulating absorption, the state of the body stores.

The author wishes to express his thanks to the Regional Physics Department of the Western Regional Hospital Board for the supply of the isotope, and to Dr. M. M. Bluhm and his colleagues of that department for a great deal of technical assistance.

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APPENDIX

Clinical Details of Cases Studied

Controls

J.McN., aged 5 years, was admitted with tuberculous meningitis from which he made a good recovery. He was under treatment with P.A.S. and I.N.A.H. at the time of the observations, and his haemoglobin was 11 g. His birth weight was 6 lb. and his weight at the time of the experiment was 40 lb. His diet appeared to have been adequate.

F.D., aged 13 months, was a microcephalic admitted with bronchitis, his physique was normal and his intelligence only moderately impaired. His weight was 16 lb. and his birth weight was 6 lb. There was no obvious evidence of malnutrition and he took his feeds well, but it was possible that having been backward, feeding may have been difficult and therefore inadequate. His haemoglobin was 10.8 g. at the time of the experiment which was started on the seventh day after admission.

J.F., aged 2 years, was admitted with a respiratory infection. She weighed 28 lb. and her birth weight was 7 lb. Her diet may have been inadequate, since mixed feeding was not instituted until 1 year of age.

Anaemic Cases

I.McL., aged 14 years, was first admitted at 7 years with pallor and was found to have an iron deficiency anaemia with a haemoglobin of 2.5 g. No adequate cause for this was found despite extensive investigations. The condition responded to oral iron but recurred on several occasions. Home conditions were poor and the diet was probably inadequate. This case differs somewhat from the others and may be considered atypical. His haemoglobin at the time of the experiment was 8.5 g.

F.O'D., aged 18 months, was admitted on account of

an upper respiratory infection and was found to have a haemoglobin of 8.4 g. His anaemia appeared to be due to three things: the fact that he was a premature baby weighing 3 lb. 11 oz. at birth, an attack of pneumonia at 6 months and delay in commencing mixed feeding until 1 year.

J.M., aged 12 months, was admitted on account of infantile eczema and transferred to the paediatric unit because of a cold in the head. His haemoglobin was 9.6 g., he weighed 20 lb. and his birth weight was 8½ lb. He had no previous history of infection and the only factor to which his anaemia could be attributed was the difficulty in feeding sometimes encountered in cases of infantile eczema.

W.D., aged 18 months, was admitted on account of stomatitis. Her weight was 23 lb. and her birth weight 7 lb. She was found to have a haemoglobin of 9.6 g. The cause of her anaemia was almost certainly nutritional as home conditions were poor.

The two remaining cases were those with the high uptakes and utilization.

M.D., aged 11 months, was admitted on account of her pallor. Her weight was 23 lb. and her birth weight 6¾ lb. Her haemoglobin on admission was 4.8 g. and the blood picture suggested a very severe iron deficiency. The cause of the anaemia in this case was almost certainly dietetic since she had been very difficult to feed. The response to oral treatment was immediate.

P.S., aged 6 years, weighed 31 lb. with a birth weight of 6 lb. He was admitted on account of pallor and his haemoglobin was 3.0 g. on admission. He was a very wilful child who refused to eat meat in any form, and it was obvious that the largely carbohydrate diet upon which he had been fed, was the cause of his anaemia. His response to oral iron was immediate.

HAEMOGLOBIN 'BARTS'— A RARE ABNORMALITY IN THE NEWBORN

BY

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(RECEIVED FOR PUBLICATION DECEMBER 9, 1959)

The study of qualitative abnormalities in haemoglobin is of fairly recent date. Two normally occurring haemoglobin variants have, however, been known for a long time: adult haemoglobin (Hb A) and foetal haemoglobin (Hb F) (Körber, 1866). They can be distinguished by alkaline denaturation, a test which has become routine practice in neonatal paediatrics (Singer, Chernoff and Singer, 1951).

About 10 years ago sickle cell anaemia was found to be due to an abnormal haemoglobin, now known as Hb S, which differs chemically from normal and is distinguished by its low solubility in the reduced state (Pauling, Itano, Singer and Wells, 1949). This decreased solubility implies a tendency to 'crystallization' (more correctly: conversion to semisolid gel) within the erythrocyte and is the cause of its sickle shape.

In the years that followed a great number of abnormal haemoglobin variants were detected, mainly among non-European people. Some of these are of great clinical significance, others are chiefly of genetic and anthropological interest. These variants were designated by the letters of the alphabet more or less in chronological order of detection.

By 1958 progress in this field had gathered so much speed, that confusion in nomenclature was likely to arise. Also, it could be foreseen that the letters of the alphabet would not suffice for all haemoglobin variants. So, when Ager and Lehmann (1958) detected a hitherto unknown abnormal haemoglobin, they named the new variant after the hospital in which the investigation had been carried out: Haemoglobin 'Barts'. This pigment was present with both Hb F and Hb A in the blood of an infant of mixed West Indian ancestry. Subsequently, about 30 infants with haemoglobin 'Barts' have been detected (Lehmann, 1959) in Mediterranean and non-European countries. This article records the second case observed in Great Britain.

Case Report

The infant's mother, I.B., aged 37 years, is a West Indian woman of negro stock. Before coming to England in 1956, she had five children born in Jamaica, of whom three are still alive. She had been married twice, the first husband, a 'white man', being the father of the first child only. The four other children had a Jamaican father.

The second of these five children died at the age of 9 days; the cause of death is not known. The fifth child was born prematurely and died when 3 days old. She does not know of any blood disease among her children, or any other members of her family.

In this country I.B. contracted a third marriage, also to a West Indian. His skin is of the same dark colour as that of I.B., but his features are not typically African and suggest the possibility of some Asian ancestry.

I.B. conceived in 1958, the date of expected delivery being June 14, 1959. The pregnancy progressed normally until 26 weeks when she had an episode of abdominal pain and vaginal bleeding. Further episodes of antepartum haemorrhage followed, necessitating admission to hospital. There, the placenta was found to be low lying, but was not considered to be praevia.

Surgical induction at 38 weeks was followed on May 27 by normal delivery of a female infant, weighing 7 lb. (3,170 g.) and measuring 20 in. (50 cm.). Her condition was only fair and in spite of the dark pigmentation the theatre sister noticed her pallor and commented on it.

Cord blood examination was carried out by the regional blood transfusion laboratory under the direction of Dr. W. Weiner, and gave the following results: blood group A, rhesus negative, direct Coombs test negative, bilirubin 0.6 mg./100 ml.

The next day the baby's capillary haemoglobin was estimated to be 94% (13.9 g.). This relatively low value was thought to be due, possibly, to transplacental blood loss. No physical abnormality was found and progress seemed to be satisfactory.

When the baby was 6 days old marked pallor and lethargy were noticed. The spleen was enlarged, but not the liver. There was no evidence of any haemorrhagic diathesis. In view of the baby's parentage it was regarded as essential to exclude sickle cell anaemia and to carry out further investigation.

Laboratory Investigation. Blood examinations were limited by the difficulty of venepuncture and had to be spread over a relatively long period.

The haemoglobin level fell from 10.8 g. (73%) on June 1, at the age of 6 days, to 8.6 g. (58%) on June 12.

A full blood count on June 16 yielded the following results: Hb 9.3 g. (63%); R.B.C. 3,580,000; W.B.C. 9,700; P.C.V. 31.5 ml.; M.C.V. 88 μ ; M.C.H.C. 30.5%.

Reticulocyte counts varied between 0.2% and 3%.

A stained blood film on June 3 revealed numerous target cells and a small number of microspherocytes; this finding was repeatedly confirmed on subsequent examinations (Fig. 1).

Sickle cells were not found in sealed wet blood film preparations, either with or without reducing agent. No inclusion bodies were seen in the red cells after 'cold incubation' with cresyl violet solution.

Haptoglobin was present in the serum. The serum iron on August 7, was 0.059 mg./100 ml.

Haemoglobin electrophoresis was carried out by Dr. H. Lehmann who demonstrated the presence of Hb 'Barts' as well as Hb A and Hb F (Fig. 2). This was confirmed on subsequent examinations.

INVESTIGATION OF THE MOTHER. A full blood count was done on June 8, with the following results: Hb. 12.0 g. (81%); R.B.C. 4,390,000; W.B.C. 5,000; P.C.V. 43 ml.; M.C.V. 98 μ ; M.C.H.C. 28%.

FIG. 1.

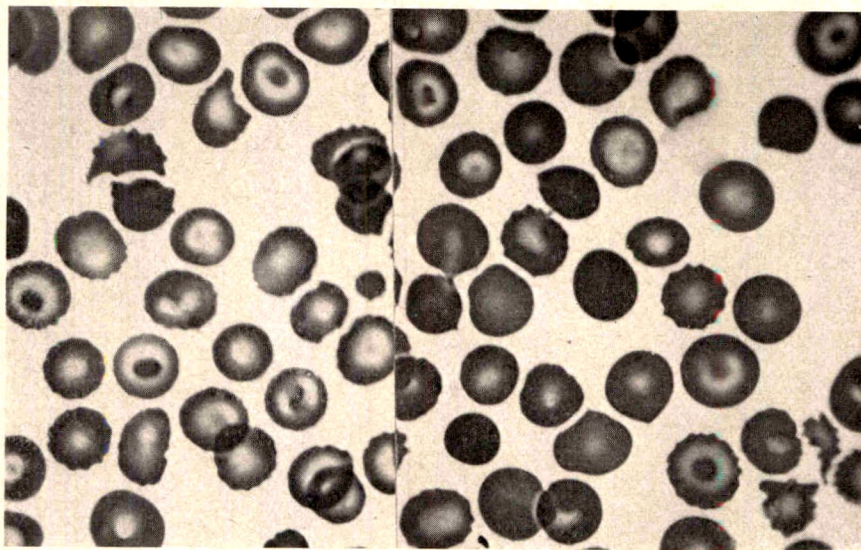


FIG. 1.—Composite picture of a blood film having numerous target cells and occasional microspherocytes.

FIG. 2.—A normal (AA) compared with Baby B. Note 'fast' Hb in baby.

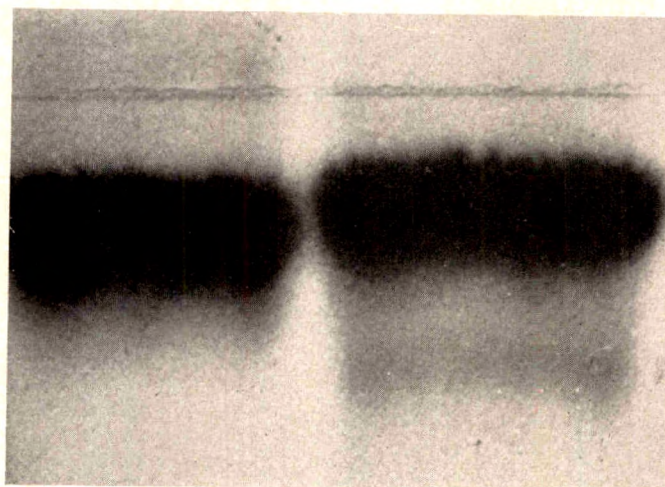


FIG. 2.

F
A

Bart's

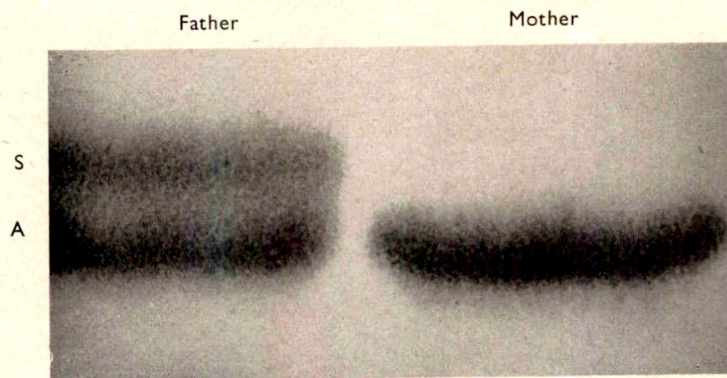


FIG. 3.—Father (AS), Mother (AA).

The stained film showed moderate regenerative activity consistent with recovery from a mild anaemia of pregnancy. No sickle cells were found. The serum iron level was 0.092 mg./100 ml.

Haemoglobin electrophoresis revealed Hb A only (Fig. 3).

INVESTIGATION OF THE FATHER. Full blood count revealed Hb 14.0 g. (95%); R.B.C. 5,700,000; W.B.C. 7,000; P.C.V. 46 ml.; M.C.V. 81 μ ; M.C.H.C. 30%.

Reticulocytes 2%. Sickle cells were found to be present after incubation with sodium bisulphite, in very large numbers.

Serum iron level 0.141 mg./100 ml.

Haemoglobin electrophoresis clearly demonstrated the presence of Hb S, as well as Hb A. The father was, therefore, confirmed as a heterozygous carrier of the sickle cell trait (Fig. 3).

Further progress. Baby B. was in reasonably good health when discharged from hospital on June 21. The haemoglobin level was then 9.0 g. (61%). The infant was seen repeatedly in out-patients and found to make satisfactory progress, but the haemoglobin level was dropping and on August 11 was as low as 7.1 g. (48%). Anti-anaemic treatment, including iron, folic acid and ascorbic acid was given. At the age of 15 weeks the total haemoglobin was 8.6 g. (58%) and haemoglobin 'Barts' was no longer demonstrable.

The infant was last seen on September 22; she was then nearly 4 months old and in good general health. The haemoglobin had risen to 9.8 g. (66%), but the blood picture was still hypochromic and microcytic. Target cells were still present and the osmotic resistance of the red cells was raised. Haemoglobin 'Barts' was absent from the electrophoretogram, but Hb F was still present, accounting for 6.8% of total haemoglobin.

Discussion

Anaemia in the new-born period can have many causes including prematurity, infection, maternal deficiency states, blood loss and haemolysis. In the present case, a contributory action of maternal deficiency anaemia and foetal blood loss cannot

be excluded. The presence of large numbers of target cells is, however, strongly suggestive of a primary abnormality of the red blood cells whilst a small number of microspherocytes may be consistent with the haemolytic character of the process.

A This anaemia was present from birth: the haemoglobin reading of 94% on the first day of life is definitely low. Moreover, pallor was noticed at birth.

The characteristic properties of haemoglobin 'Barts' were summarized by Lehmann and his colleagues (Ager, Hunt, Kohler and Lehmann, 1959). Here we draw attention to only some of its peculiarities:

(1) Both in the process of electrophoresis and of chromatography 'Barts' is one of the fastest moving haemoglobin variants so far known. Its position relative to other haemoglobins varies with the particular method used and with the pH of the buffering medium.

(2) Spectroscopically, 'Barts' is closely similar to foetal haemoglobin and shows the tryptophan band, which is characteristic of Hb F.

(3) Hb 'Barts' is less resistant to alkali denaturation than Hb F, but more so than Hb A.

(4) Hb 'Barts' tends to disappear, with progressing age, from the infant's blood much in the same way as 'normal' foetal haemoglobin does.

An apparent exception to this last-mentioned rule was recently discovered in a child whose 'Barts' had persisted beyond infancy. This child was found to be homozygous for thalassaemia (Choremis, Zannos-Mariolela, Ager and Lehmann, 1959).

Heredity. As haemoglobin 'Barts' is associated with infancy, there is no hope of finding any evidence of it in the parental electrophoretogram. Genetic investigations, which play so great a part in the study of other haemoglobinopathies, have so far failed to yield any positive results. This does not imply that we shall necessarily have to wait until those few infants with 'Barts', who are known at present, reach the reproductive age. Genetic information may be forthcoming from observation of their younger siblings. Where, in addition to true sibs, half-brothers and half-sisters are available for investigation, the possibilities of study are wider. In the present case history, I.B. with her three sets of

families almost fulfilled conditions designed for laboratory experiments and our regret of not being able to investigate her previous children is so much greater. We shall, of course, try to keep her under observation in any future pregnancies.

The finding of a heterozygous sickle cell trait in the father is an interesting observation, but in the light of our present knowledge this fact is unconnected with the infant's haemoglobinopathy.

Summary

Haemoglobin 'Barts' was found in the blood of an anaemic West Indian newborn girl. No evidence of this abnormal haemoglobin variant was found in either parent, but the father was heterozygous for Hb S. By the age of 15 weeks 'Barts' could no longer be demonstrated in the infant's electrophoretogram. This is the second case found in this country.

This paper could not have been written without the generous help given by Dr. Hermann Lehmann, who not only carried out the crucial diagnostic tests, but also

guided us in the investigation and instilled into us some of his own enthusiasm. We are indebted to Dr. Ben Wood for permission to publish and to Dr. M. J. Meynell for help and advice. We owe thanks to Mr. W. R. Lea, F.I.M.L.T., for the microphotograph of Fig. 1. and to Mr. William Johnson, F.I.M.L.T., who took great pains in performing most of the routine examinations.

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SYSTEMIC LUPUS ERYTHEMATOSUS IN PREGNANCY WITH HAEMOLYTIC ANAEMIA, LEUCOPENIA AND THROMBOCYTOPENIA IN THE MOTHER AND HER NEWBORN INFANT

BY

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Pregnancy in a patient with systemic lupus erythematosus is not extremely rare. However, very few reports dealing with the simultaneous occurrence of the disease or some of its manifestations in the mother and her newborn infant have been published. In the University Hospital, Oslo, we have observed a young woman with subacute systemic lupus erythematosus, whose newborn son for some time after birth presented haematological changes similar to those of his mother, probably due to passage of antibodies across the placental barrier.

Case Report

A housewife, 29 years of age, developed generalized lymphadenopathy, leucopenia and elevation of the erythrocyte sedimentation rate in February, 1958, during her fourth pregnancy. She had had an abortion in 1952 and a miscarriage in 1957. In 1953 she gave birth to a child who is living and well. In January, 1958, she was inoculated with BCG vaccine because her husband had contracted a tuberculous infection. She remained in fairly good condition until the beginning of July, 1958, when proteinuria, haematuria and anaemia developed. She was then admitted to the local hospital, where normal, spontaneous delivery took place on July 14, 1958.

Following delivery the patient developed a high, fluctuating fever which was not influenced by treatment with antibiotics in large doses. Her general health was poor and she suffered from pains in the chest and shoulders. Marked leucopenia with moderate eosinophilia was present. The haemoglobin dropped to about 7 g. %, and there were obvious signs of increased haemolysis: reticulocytosis and a positive Coombs test. Two blood transfusions had only transient effect and she was transferred to Medical Department A, University Hospital, Oslo, on October 4, 1958, while her 12-week-old infant was admitted to our department.

On admission she was in poor condition with high

fever, emaciation and pallor. Her haemoglobin level was 7 g. %, but there were no longer signs of increased haemolysis. The Coombs test was only weakly positive. A weak red cell antibody, probably of the 'cold' type, could be demonstrated in her serum. She still had a persistent leucopenia with a minimum white cell count of 1,500 per c.mm. There were 171,000 blood platelets per c.mm. Erythrocyte sedimentation rate remained high, up to 133 mm., during her stay in the hospital. Her urine contained about 0.1% protein. Electrophoretic determination of the serum proteins showed a marked decrease in albumin (1.8 g. %), and a considerable increase in gamma globulin (3.3 g. %). Typical L.E. cells could be demonstrated and a diagnosis of subacute systemic lupus erythematosus was made. Under treatment with corticosteroids she made good progress, and was discharged on November 19, 1958. She is now receiving 10 mg. prednisone daily as a maintenance dose and is able to do her housework.

Her newborn infant looked somewhat pale at birth but otherwise appeared normal. He seemed to thrive fairly well on cow's milk during his first weeks of life. Because of the mother's illness he remained in the local hospital. After a few weeks his paleness attracted the nurse's attention. However, haematological studies were not performed until he was two months of age, when his general health seemed to be deteriorating. His haemoglobin level was then found to be 3.3 g. %; a few days later it was 2.5 g. %; erythrocytes 1.23 m./c.mm.; reticulocytes, 22.8%; leucocytes 1,800/c.mm. Bone marrow smears showed marked erythroid hyperplasia. Within two weeks five transfusions of whole blood had to be given, 500 ml. in all, but there was only transient effect on the haemoglobin level. A Coombs test, performed after the first blood transfusions were given, was equivocal.

He was transferred to the University Hospital, Oslo, on October 4, 1958, when 12 weeks old. He was slightly jaundiced with serum bilirubin 2.4 mg. %. His spleen was moderately enlarged. He had just received a blood transfusion, which had brought his haemoglobin up to 10.3 g. %. The white cell count had risen to 5,900,

the differential count was normal, blood platelets 114,000. L.E. cells could not be demonstrated. The Coombs test was now negative.

In three days his haemoglobin dropped to 5.8 g., and his reticulocyte count rose to 13.3%. He was given a transfusion of 100 ml. whole blood, but three days later his haemoglobin level had once more fallen to 5.6 g. On October 11, treatment with prednisone was begun. He was given 10 mg. per day in divided doses. Within two weeks the blood picture had become completely normal. The dosage of prednisone was gradually reduced and the medication was terminated on November 10, 1958, since when he has remained quite well with a normal blood picture.

Except for the haematological changes we could find no signs of systemic lupus erythematosus in this patient. An electrophoretic determination of his serum proteins revealed a gamma globulin level of 1.2 g. %, which is relatively high for an infant 3 months of age. Otherwise the serum proteins were normal. He was group 0 Fy(a-) E- S- Le(a+) Rh+ (R₁r), his mother A₁ Fy(a-) K- S+ Le(a-) Rh+. No antibodies against the infant's red blood cells could be demonstrated in the mother's serum, and no platelet antibodies could be detected in either the mother's or the infant's serum (Dr. J. Lundevall). Technical facilities for studying leucocyte antibodies or foetomaternal leucocyte incompatibility were not available.

Discussion

In short, the case history reported was as follows: a woman, 29 years of age, became ill with subacute systemic lupus erythematosus during her fourth pregnancy. At the time of delivery an exacerbation of the disease occurred with haemolytic anaemia, positive Coombs test, leucopenia and possible thrombocytopenia. Her newborn infant developed similar haematologic manifestations, which, however, disappeared at 3½ months of age following treatment with blood transfusions and prednisone.

Pregnancy may be a serious complication to systemic lupus erythematosus, especially in the acute cases, with high maternal and foetal mortality. Ellis and Berenson (1952) collected a series of 69 cases from the United States, 56 with acute and 13 with subacute systemic lupus erythematosus. Treatment with corticosteroids had not been introduced at the time these patients were seen. Among the 56 acute cases 14 deaths were recorded in connexion with the pregnancy, and in addition 11 patients became worse. In the offspring there were 10 deaths *in utero* and six in the neonatal period. Among the 13 women with the subacute form of the disease there were no deaths in connexion with pregnancy or delivery, and a few of them even showed some improvement. In six the pregnancy terminated with abortion, while the other seven gave birth to living, apparently healthy infants. In chronic

discoid lupus erythematosus, pregnancy does not seem to involve special hazards for mother or child.

Our knowledge about the causes of foetal or neonatal death as a result of maternal systemic lupus erythematosus is scanty. Hogg (1957) has described the necropsy findings in an infant who died on the second day of life, and who seemed to have signs of congenital systemic lupus erythematosus with typical vascular lesions. This child also had subendocardial fibroelastosis. Based on this observation Hogg advanced the hypothesis that subendocardial fibroelastosis may in some cases be due to a collagen disease. Other cases of congenital forms of the disease have not been reported. But Bridge and Foley (1954), and later other authors (Berlyne, Short and Vickers, 1957; Mijer and Olsen, 1958), were able to demonstrate placental transmission of the L.E. factor to the newborn infant. The L.E. test in these cases remained positive in the infant's blood until about 7 weeks of age, and then became negative. It is not surprising that this factor, being a gamma globulin, can pass the placental barrier.

Haematological manifestations in a newborn infant as a result of maternal systemic lupus erythematosus have not been previously reported. However, this may be partly due to the fact that they have not always been adequately searched for. We do not know precisely when our patient developed his pancytopenia. He looked pale even at birth. His paleness gradually increased, but his blood picture was not studied until he was 2 months old. A severe haemolytic anaemia and a marked leucopenia were then discovered. Blood platelets were not counted at that time. On admission to our department, when he was almost 12 weeks old, increased haemolysis could still be demonstrated. The leucopenia, however, was no longer present. A moderate thrombocytopenia with 114,000 blood platelets per c.mm. was found.

The fact that the patient has remained healthy and kept a normal blood picture since the age of 3½ months strongly supports the concept that his haematologic changes were caused by antibodies transferred from the mother. One must suppose (1) that the pancytopenia of this young woman with systemic lupus erythematosus was due to circulating antibodies, and (2) that there was placental transmission to the infant of these antibodies affecting erythrocytes, leucocytes and thrombocytes.

A similar mechanism is known to operate in chronic idiopathic thrombocytopenic purpura. About 60% of infants born of mothers with this disease get a transient thrombocytopenia, lasting for

about two to four months after birth (Epstein, Lozner, Cobbey and Davidson, 1950; Nelson, 1954) and caused by placental transmission of maternal platelet antibodies.

Passage of red cell antibodies across the placental barrier is of course seen in erythroblastosis foetalis. In this disease, too, the haemolytic process may last for about three months. The occurrence of transient haemolytic anaemia in an infant born of a mother with autoimmune haemolytic anaemia, as in our case, has hitherto not been unequivocally demonstrated (Dacie, 1954; Söderhjelm, 1959), but might perhaps have been present in the case reported by Söderhjelm.

Transient leucopenia (granulocytopenia) in the neonatal period has been described in two siblings (Slobody, Abramson and Loizeaux, 1950; Lehdorff, 1951; Luhby and Slobody, 1956), but must be rare. The two siblings reported by Slobody and co-workers showed a marked granulocytopenia on the third day of life, with complete restitution in three to four weeks. The mother's blood picture was normal; leucocyte antibodies could not be demonstrated. Still, these authors advance the theory that the granulocytopenia might have been elicited by foetomaternal leucocyte incompatibility through a mechanism similar to that of the anaemia in haemolytic disease of the newborn. Payne and Rolfs (1958) have shown that multiparous women have a higher incidence of leucocyte antibodies in their serum than do those who have not been pregnant, a finding which may be due to foetomaternal leucocyte incompatibility. However, they report that so far not a single case of consequent neonatal leucopenia has been found. Simultaneous occurrence of leucopenia in a mother and her newborn infant has been reported in two families by Stefanini, Mele and Skinner (1958). In these cases the mothers were suffering from chronic neutropenia. The infants' blood picture became normal in three to four weeks after birth. In one case leucocyte antibodies could be demonstrated in both the mother's and her newborn infant's serum.

It has been assumed (Dausset, 1956) that the leucopenia in systemic lupus erythematosus may be caused by the presence of the L.E. factor which, as mentioned above, may pass the placental barrier. However, in newborn infants with a positive L.E. test hitherto reported in the literature, leucopenia has not been demonstrated. One cannot be certain whether it has not been present, or whether it has been overlooked.

Summary

A woman of 29, developed signs of subacute systemic lupus erythematosus during her fourth pregnancy. In connexion with delivery an exacerbation of the disease occurred with pronounced haemolytic anaemia, a positive Coombs test, leucopenia, and a mild thrombocytopenia. Her newborn infant also developed a severe haemolytic anaemia, leucopenia and thrombocytopenia, but with complete restitution at 3½ months of age following treatment with blood transfusions and prednisone.

Placental transmission of the L.E. factor has been observed by several authors. A single case interpreted as congenital systemic lupus erythematosus has also been reported. But pancytopenia in a newborn infant caused by systemic lupus erythematosus in the mother does not seem to have been described before. The infant's haematological manifestations may be due to the passage of maternal antibodies against the formed elements across the placental barrier.

Infants born of mothers suffering from this should have their blood picture checked during the first months of life, particularly if the mother shows prominent haematological changes.

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PANCYTOPENIA WITH CONGENITAL DEFECTS (FANCONI'S ANAEMIA)

BY

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Fanconi (1927) drew attention to a syndrome of pancytopenia associated with congenital defects which has since become known as Fanconi's anaemia. Reports of other cases followed from different parts of the world, including one from South Africa (Kessel and Cohen, 1953), but the condition remains a rare one.

We report here five cases of pancytopenia with accompanying congenital anomalies, seen in Cape Town. Some unusual features are mentioned and it will be shown that the syndrome may not be recognized when the associated defects are inconspicuous.

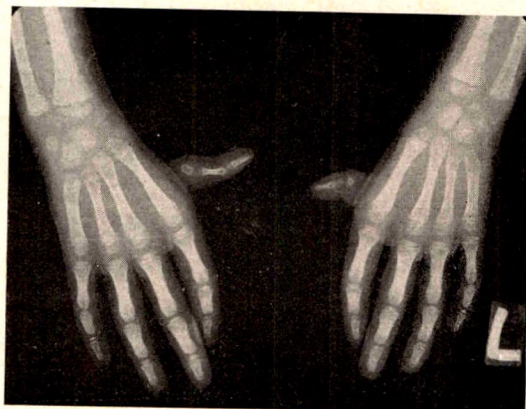
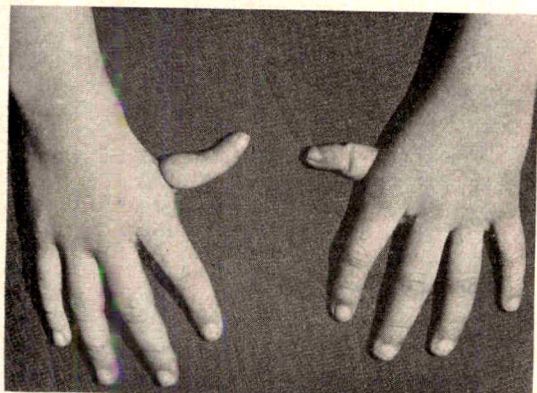
Case Reports

Case 1. D.G., a white boy, was first admitted to Groote Schuur Hospital in January, 1951, at the age of 6 years.

From the age of 14 months he had had recurrent attacks of bronchitis. He had also undergone tonsillectomy, right inguinal herniotomy and dilatation for anal stenosis. For three months before admission he had been pale, anorexic and irritable.

His parents were in good health. Their first child, a girl, was said to have had unilateral polydactyly on the radial side, persistent patency of the ductus arteriosus and subacute bacterial endocarditis and had died at the age of 6 years.

During the patient's 20 admissions to hospital the following features were recorded: he was pale and underweight for his age, weighing 33 lb. at 6 years, and was judged to be of normal intelligence. Microcephaly—head circumference was 19½ in. at 8 years; microphthalmia, absent testes and hyperpigmentation of the skin were noted. Both thumbs were grossly deformed (Fig. 1) and attached to his hands by soft tissue only. Radiographs showed maldevelopment of the metacarpals and phalanges of the thumbs and retarded ossification of the carpal bones (Fig. 2). The radial pulse was not palpable at either wrist, but the pulsation of the ulnar arteries was forceful. Femoral artery pulsation was normal. A systolic murmur, maximal in the pulmonary area, was heard at each admission. A systolic thrill in the second and third left interspaces and in the neck was occasionally recorded, but radiographs of the chest, screen examination of the heart and electrocardiogram were thought to be within normal limits.



FIGS. 1 and 2.—D.G., aged 7 years. Note abnormality of thumbs and delayed ossification of carpal bones.

The original blood findings were as follows: Haemoglobin was 7.3 g.%; the peripheral blood smear showed anisocytosis and poikilocytosis of the red cells; white cells numbered 12,250/c.mm., of which 80% were lymphocytes, 18% neutrophils, 1% monocytes and 1% eosinophils; his blood group was A Rh positive and his E.S.R. 34 mm. (Westergren) in the first hour. Bone marrow in January, 1953 was normal and a platelet count at the same time was 142,000/c.mm. Reticulocyte counts varied between 0.5 and 5%.

The anaemia was unresponsive to haematinics and was uninfluenced by splenectomy, which was performed in April, 1953. Blood transfusions became necessary at increasingly short intervals. In June, 1955 he was admitted for blood transfusion and shortly afterwards developed pneumococcal meningitis from which he died. The occurrence of petechial cutaneous haemorrhages is first recorded at this time, when a platelet count was 3,000/c.mm. No autopsy was performed.

Case 2. R.W., a white girl, was first admitted to Groote Schuur Hospital in July, 1953 at the age of 6 years.

It was not made known to us at the time that a supernumerary thumb had been amputated when she was 18 months old. Since the age of 3 her parents had noticed that she bruised very easily and she had had recurrent respiratory infections, each temporarily responsive to sulphadiazine, of which her father, a farmer, kept a stock primarily intended for veterinary use. Increasing pallor, fatigue and weight loss had been noticed for two months.

Both her parents and three younger siblings were reported to be well, although it was recalled that her mother had been anaemic in her youth.

On examination the child was judged to be of normal intelligence. She was pale and thin, weighing 40 lb. and petechial haemorrhages were noted in skin, mucous membrane of pharynx and ocular fundi. The Hess test for capillary fragility was positive. A soft systolic murmur, maximal at the cardiac apex, was constantly heard throughout her subsequent admissions. A mid-diastolic murmur, described as blowing in character, was recorded at her first admission and again six months later, but on no other occasion.

The peripheral blood showed a haemoglobin of 4.5 g.%. The smear showed anisocytosis and poikilocytosis of the red cells, and the white cells were 1,360/c.mm. (lymphocytes 78%, neutrophils 16%, staff cells 4%, monocytes 1% and eosinophils 1%). The platelet count was 8,000/c.mm., reticulocyte count 1.8%, E.S.R. 95 mm. (Westergren) in the first hour and the blood group A Rh positive. The bone marrow, frequently examined, was thought on one occasion to show megaloblastic hyperplasia, but on all other occasions, apart from the constant observation that platelets were scanty and megakaryocytes absent, it was thought to be normal. Radiographs of chest, pelvis and long bones, screen examination of the heart, electrocardiogram, blood Wasserman reaction, osmotic fragility of red cells, serum bilirubin, direct Coombs test, Paul-Bunnell test, liver function

tests, plasma proteins, fractional test meal and intravenous pyelogram all resulted in normal findings.

A diagnosis of anaemia, neutropenia and thrombocytopenia, possibly due to sulphonamide toxicity, was made and during 14 subsequent admissions there was no reason to alter it. In retrospect, however, it should be mentioned that tendon reflexes were noted to be brisk on more than one occasion, that generalized hyperpigmentation of the skin was noticed at her 12th admission, and that pyuria was a frequent finding, suggesting that there might have been some slight renal anomaly not demonstrated by intravenous pyelography.

The majority of her admissions were on account of gross anaemia with which epistaxis and infections were often associated. Neutropenia and thrombocytopenia were constant findings. Prolonged courses of A.C.T.H., cortisone, prednisone, vitamin B₁₂, folic acid and iron were without benefit, as was splenectomy, performed at her seventh admission in October, 1954. Blood transfusion and antibiotics were the only effective forms of treatment, and, at the last, even these failed. She died of staphylococcal pyaemia with widespread haemorrhagic manifestations, pneumonia and jaundice in August, 1957. No autopsy was performed.

Case 3. Ju.W., younger sister of R.W., was admitted in May, 1959, at the age of 11 years.

For the preceding year increasing pallor and a tendency to bruise easily had been noted by her parents. Six weeks before coming under our care she had been admitted to hospital near her home with a sudden onset of fever accompanied by flitting pains in the knees and ankles. The fever and joint pains were short lived, but her anaemia proved unresponsive to oral and intramuscular iron and to vitamin B₁₂ and she was transferred to Cape Town for further investigation.

Her parents and three younger brothers were reported to be in good health.

On examination she was a well grown and intelligent girl weighing 74 lb. Pallor of mucous membranes, a rather darkly pigmented skin and a short, soft systolic murmur, which was loudest at the lower left sternal border, were the only abnormal physical findings detected.

The haemoglobin was 7.5 g.%; the smear showed marked anisocytosis and poikilocytosis of the red cells; the white cells numbered 7,000/c.mm., of which 94% were lymphocytes and 6% neutrophils. Platelets were scanty, the platelet count being 58,000/c.mm. E.S.R. was 36 mm. (Westergren) in the first hour and her blood group A Rh positive. Two attempts at bone marrow aspiration having failed to produce more than a few marrow cells, a bone biopsy was obtained by trephine from the iliac crest. This specimen was pale, with scanty marrow cells, which appeared to be normal and to be present in normal proportions. Radiographs of chest and long bones and an electrocardiogram showed no abnormality. Blood culture was sterile, the Mantoux test negative and the urine normal.

Folic acid 10 mg. twice daily was given for 10 days without benefit. Two pints of blood were transfused and she was sent home.



FIG. 3.—Jo.W., aged 7 years. Note abnormal thumbs; Ju.W. aged 11 years, note difference in size of thenar eminences.

It was felt that the occurrence of hypoplastic anaemia, neutropenia and thrombocytopenia in the two sisters must have either a genetic or an environmental cause. Moreover it was suggested by their father in a letter to us that his three sons were beginning to look pale. Their private doctor kindly sent oxalated specimens of blood and examination of these revealed that one, that of Jo.W. (Case 4), was frankly abnormal. In order to search for any possible environmental influence, one of us (B.G.) arranged to visit the farm, 200 miles away, where the family lived in a region of hot springs. The findings were as follows: (1) Scrutiny of the environment with a Geiger counter failed to reveal any source of excessive ionizing radiation. (2) Investigation, including chemical analysis of the farm water, failed to reveal any source of chemical poisoning. (3) Jo.W. was found to have abnormal thumbs incapable of active abduction, adduction or extension and Ju.W. was re-examined and found to have a right thenar eminence smaller than her left and to be incapable of abducting or extending the right thumb. (Fig. 3). (4) It was now learnt that mother and father were distantly related and that R.W. had had a supernumerary thumb amputated at an early age.

A diagnosis of Fanconi's anaemia could now be made and Ju.W. and Jo.W. were asked to return to us for further investigation.

Ju.W. (Case 3) was readmitted in July, 1959. Her haemoglobin, which was 12 g.% on her discharge six weeks previously, had dropped to 7.5 g.%. The cutaneous hyperpigmentation, noted at her first admission, was confirmed by several observers and became more pronounced when her anaemia was again corrected by blood transfusion. There were numerous bruises on her arms and legs and her knee and ankle jerks were very brisk. The significance of slight gynaecomastia was felt to be uncertain in view of her age. Radio-

graphs of her hands showed that the metacarpal and proximal phalanx of her right thumb was of equal length but more slender than that of her left thumb. Intravenous pyelography showed no abnormality.

Case 4. Jo.W., aged 7 years, brother to R.W. and Ju.W., was admitted in July, 1959.

Slight pallor and a tendency to bruise readily had been observed for about three months.

On examination there was the striking abnormality of both thumbs already mentioned. He weighed 44 lb. and his intelligence was thought to be normal. Slight hyperpigmentation was confined to the skin of the axillae. There was some bruising on the legs and arms. Radial pulses were not palpable at either wrist, but the ulnar pulsation was forceful. A short, soft systolic murmur, maximal at the apex, was heard but there was no other evidence of heart disease. The tendon reflexes in the legs were accentuated.

The haemoglobin was 10 g.%; the red cells showed anisocytosis and poikilocytosis; white cells numbered 4,000/c.mm., of which lymphocytes comprised 98% and neutrophils 2%. His blood group was AB Rh positive and the E.S.R. was 35 mm. (Westergren) in the first hour. Very few platelets were seen on the peripheral blood smear, the count being 49,000/c.mm. Three attempts at bone marrow aspiration from different sites produced only scanty marrow cells and further measures to obtain a specimen of marrow were not thought justifiable. Radiographs showed spina bifida of the 6th cervical and 3rd thoracic vertebrae in addition to maldevelopment of the metacarpals. Intravenous pyelography was normal.

Case 5. P.v.d.W., a white boy, first came under our care in January, 1957, when he was 6 years old.

At the age of 18 months he had had a bifid uvula repaired. Apart from chicken pox he had been well until the age of 4 years when excessive bruising and frequent epistaxes commenced. Fatigue and dyspnoea had been noticed for one week prior to admission. His parents and six siblings were said to be healthy.

He was a fair haired boy of average intelligence weighing 41 lb. Numerous bruises were noted, although the Hess test for capillary fragility was negative. His skin was rough and dry and his finger and toe nails were dystrophic. Bilateral epiphora was present due to blockage of both lacrimal ducts. This was improved by probing, but soon recurred and resisted further treatment. A soft, systolic murmur, present at each subsequent admission, was heard at the cardiac apex and lower left sternal border.

His haemoglobin was 5.5 g.%, the red cells showed anisocytosis, poikilocytosis and some polychromasia and the white cells were 4,500/c.mm. Lymphocytes numbered 72%, neutrophils 14%, staff cells 2%, monocytes 7% and eosinophils 5%. Platelets were very scanty, there being only 10,000/c.mm. His blood group was A Rh positive and the E.S.R. 70 mm. (Westergren) in the first hour. Other investigations were: reticulocyte count 4%; bleeding time eight minutes; coagulation time (Lee and White) seven minutes; prothrombin index 100%; thromboplastin generation test abnormal in a manner consistent with thrombocytopenia and clot retraction normal.

The following additional tests resulted in normal findings: Paul-Bunnell, Widal and brucella agglutination tests, blood Wassermann reaction, blood culture, serum bilirubin, direct Coombs test, osmotic fragility of red cells, plasma proteins and radiograph of chest. Mantoux testing was negative and the urine normal.

Radiographs of long bones showed some widening of the medullary cavities consistent with marrow hyperplasia, which was a constant finding in this case. The bone marrow showed normal erythropoiesis and granulopoiesis apart from some normoblasts suggestive of iron deficiency; platelets were scanty and megakaryocytes were not seen.

Ferrous sulphate 180 mg. was given three times daily and the haemoglobin level rose in three weeks to 10 g.%, reticulocyte counts remained high and platelet counts low. He was discharged on oral iron and was seen again three months later for review when the findings were unchanged except that the reticulocyte count had fallen to a normal level and iron deficiency normoblasts had disappeared from the bone marrow.

Nine months later he was readmitted with gross anaemia. Immediate blood transfusion raised the haemoglobin level to 11.5 g.% and prednisone 5 mg. four times daily was then commenced and given for five weeks. This had no effect on the persistently low platelet count, but it was thought possible that a haemolytic aspect of the disease might have been inhibited because, while prednisone was being administered, the haemoglobin level rose steadily to 12.5 g.%. He was discharged again to his home in the country but within a month he was readmitted with extreme pallor. On

this occasion he was not transfused. Prednisone was again commenced and after one week oral iron and ascorbic acid were added. Despite the fact that reticulocyte counts remained slightly above normal and the bone marrow continued to show active erythropoiesis, three weeks of this treatment resulted in no rise of haemoglobin. Splenectomy was now performed and one week post-operatively the platelets numbered 332,000/c.mm.

He now remained well for four months, but then again began to complain of dyspnoea and fatigue on exertion. He was readmitted in February, 1959, grossly anaemic and it was found that thrombocytopenia had recurred. Following blood transfusion, prednisone and iron therapy were again tried but without benefit and he was thereafter readmitted for blood transfusion at intervals of approximately six weeks, neutropenia and thrombocytopenia remaining constant findings. On his final admission to hospital he was bleeding into his gastrointestinal and renal tracts as well as into the skin. Blood transfusion failed to control the bleeding and he died on August 22, 1959.

Discussion and Review of the Literature

The disease may be familial, as in Fanconi's original cases, and is then thought to be inherited as a recessive trait (Reinhold, Neumark, Lightwood and Carter, 1952). It may occur sporadically, for which a gene mutation is believed to be the explanation (Dawson, 1955). We have been able to find full descriptions in the literature of 30 cases occurring in 16 families and of 13 cases occurring sporadically.

The Congenital Abnormalities. A list of the congenital abnormalities more commonly associated with the syndrome is set out in the Table. This

TABLE
CHIEF CONGENITAL DEFECTS IN 43 CASES OF THE FULL SYNDROME

Abnormality	Cases
Pigmentation	36
Abnormalities of thumbs	23
Shortness	22
Microcephaly	19
Hypogonadism	15
Hyperreflexia	13
Renal abnormalities	13
Microphthalmia	9
Mental retardation	9
Squint	9
Delayed ossification centres	7
Ear abnormalities	7
Heart abnormalities	6

includes our own cases and is an amplification of a similar one drawn up by Dawson (1955). Hyperpigmentation of the skin, the commonest abnormality, was found in four of our patients. Deformities of thumbs, and sometimes also of the radii, were frequent findings; the former anomaly

was present in four of our cases. Several authors commented on delay in the appearance of the ossification centres in the carpal bones; this anomaly we found only in our first case. Shortness of stature, hypogonadism and abnormalities of the nervous system, including mental retardation and hyperreflexia, were not infrequently reported as were renal anomalies. The last took the form of a single kidney (Kunz, 1952; Levy, 1952; Reinhold *et al.*, 1952; Kessell and Cohen, 1953; Cowdell, Phizackley and Pyke, 1955; Dawson, 1955); ectopic position of one kidney (Beautyman, 1951; Francis, Moir and Swift, 1955) and, in one case, a horse-shoe kidney (Dacie and Gilpin, 1944). Congenital cardiac anomalies were occasionally found. All our cases had systolic murmurs, which persisted after transfusion, but further cardiological investigation was not suggestive of any specific abnormality. We are not sure, therefore, whether the murmurs were indicative of some minor cardiac pathology or not. One of our children had a partial spina bifida of a cervical and a thoracic vertebra. This occurred in one of Shaw and Oliver's cases (1959), while Lynch, Sherman and Elliott (1954) stated that they had heard of a child with pancytopenia and this associated anomaly. A feature, found in two of our cases, which we have not seen mentioned elsewhere, was the fact that the radial pulses could not be felt. If Case 5 (P.v.d.W.) is accepted as belonging to the syndrome, his anomalies are yet others to add to the list.

The Blood Picture. In the protocols consulted, all patients had greatly reduced platelet counts and in most cases there was a leucopenia especially affecting the neutrophils. Variation in size, shape and colour of the red cells was common. Reticulocyte counts varied from less than 1% in many cases to quite high levels in others. In cases in which the sedimentation rate was reported this was nearly always considerably raised, but as there was usually an accompanying anaemia the significance of this finding is uncertain. The bone marrow, sometimes initially described as normal, eventually nearly always showed reduced numbers of all blood forming elements.

Age of Onset and Sex Distribution. The more obvious defects are usually noticed soon after birth though some are not apparent until later. Anaemia is not usually manifest until after 6 years of age, although its onset has been reported both earlier and later than this. There are cases on record where the anaemia only became apparent in adult life (Rohr, 1949; McAlpine, 1954; Cowdell *et al.*, 1955). On the other hand, Emery, Gordon, Rendle-

Short, Varadi and Warrack (1957) have reported two infants dying in the neonatal period. Both had haemorrhagic manifestations with scanty platelets and in both cases the radii were absent. They quoted five similar cases from the literature. All were sporadic in origin. Shaw and Oliver (1959) have recently given an account of the same blood and skeletal defects in two siblings in the first months of life. These findings indicate that the anaemia may, on occasion, occur in extreme youth in both the sporadic and familial types of Fanconi's anaemia.

In the cases we have studied or read about, 43 in all, the disease occurred twice as often in boys (29) as in girls (14), but as the numbers are small it is not certain if this is the true sex incidence.

Variants. There appear to be possible variants of the syndrome. Estren and Dameshek (1947) described two families in which three and five members respectively died from hypoplastic anaemia. Though none of these had associated anomalies, their familial nature would seem to link them with Fanconi's anaemia.

In another report Cowdell *et al.* (1955) tell of two brothers both of whom had typical congenital defects. One of them showed anaemia at the age of 22 years; the bone marrow was hypoplastic and he died one year later. The other brother developed leukaemia when 27 years of age. This suggests another direction in which the disease may show itself.

Treatment and Prognosis. There is no known curative treatment. All types of haematinics have been tried and steroids have been used in some of the cases reported (Kunz, 1952; Kessell and Cohen, 1953; Francis *et al.*, 1955) as well as by ourselves. No real benefit has resulted from any of these forms of treatment. In a few cases it has been claimed that splenectomy has improved matters, particularly when the reticulocyte count has been high, but for the most part the course of the disease has been uninfluenced. There was no improvement in our three patients who had their spleens removed. Repeated blood transfusion is the only means by which definite temporary improvement can be effected. Intervals between transfusions become progressively short and eventually blood has to be given about every two months and sometimes more frequently.

The disease is invariably fatal, with the single exception of Dawson's (1955) case of a girl first seen with anaemia at 10 years of age. At the age of 20 she was reported to be alive, well and married. The usual duration of illness is from a few months

to several years, the average life expectancy being two to four years after the first appearance of anaemic symptoms. In most cases death has been due to infection or massive haemorrhage.

Fanconi's anaemia should be considered in the differential diagnosis of all cases of pancytopenia. A careful examination for congenital defects, however minor, should be made and other members of the family should be investigated for signs of the trait. If this is not done the syndrome may not be recognized, as occurred in the first two members of the family we have described. It was only when the third child was seen that the correct diagnosis was made and the significance of barely noted defects in his sisters was appreciated.

Summary

Four cases of Fanconi's anaemia are presented as well as a fifth case which it is suggested may be another example of this condition.

That the disease may not be recognized if the associated congenital defects are minor ones is exemplified in two out of three cases found in one family.

The literature is reviewed and the congenital defects which commonly occur are listed and discussed including some unusual manifestations in our cases.

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Addendum

When this article was submitted the paper by Shahidi and Diamond (1959) on the treatment of aplastic anaemia with a combination of testosterone and steroids had not yet appeared.

Our two surviving children are now being treated in this way and the results will form the subject of a future communication.

STUDIES IN HIRSCHSPRUNG'S DISEASE

BY

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The morbid anatomy of Hirschsprung's disease is now firmly established. Swenson and Bill (1948) noted that the dilated colon which figures so largely in the earlier description of the disease terminated at a point proximal to the anus and was followed by a spastic segment. They concluded that the obstruction was due in some way to this segment and that the hypertrophy and dilatation of the bowel above was secondary to this obstruction.

Further work by Zuelzer and Wilson (1948), Bodian, Stephens and Ward (1949), Whitehouse and Kernohan (1948) and Swenson, Rheinlander and Diamond (1949) has shown that in the narrowed spastic segment there is a complete absence of the ganglion cells which form Meissner's and Auerbach's intramural plexuses. Instead there are large bundles of non-medullated nerve fibres occupying the position of the plexuses. This aganglionic segment extends from the anus up to the dilated part of the bowel. Examination of the dilated colon itself shows that there is hypertrophy of the muscle walls, but that the intramural ganglion cells are present in the normal quantities and arranged in the normal manner.

The abnormalities of function of this aganglionic segment are less clearly defined. Barium enema shows that this segment extends from the anus to the rectosigmoid junction or distal sigmoid colon; it appears narrow and can sometimes be seen to undergo segmentation. Proximal to this segment the bowel enlarges to form the typical megacolon. Using a technique which involves the recording of intracolonic pressures by means of multiple balloon at various levels in the lower bowel, Swenson *et al.* (1949) showed that there was increased tone with an absence of normal peristalsis in the narrowed segment. Davidson, Slesinger, Steinberg and Almy (1955) described the effect of mecholyl on the activity of the colon in Hirschsprung's disease as recorded by catheters in the lumen of the gut. They noted that in records taken from the aganglionic segment of six patients with Hirschsprung's disease, mecholyl produced no

change; whereas in 20 normal subjects there was no change in 11, and relaxation of the bowel in nine. In discussing their results they noted the possibility of using this method for mapping out the aganglionic segment of intestine, and they also commented on the absence of any increased sensitivity of the intestine to cholinergic drugs, such as is found in the aganglionic part of the oesophagus in achalasia of the cardia, and such as would be expected from Cannon's law of denervated structures. They conclude that this is due to the lesion being congenital rather than acquired.

It seemed that there was room for further investigation of the changes in the colon which occurred in Hirschsprung's disease. In the experiments which are described below, various properties of intestinal muscle obtained at operation from the aganglionic segment of gut from patients with Hirschsprung's disease and from a similar region in normal controls were examined to determine more accurately the nature of the derangement of function.

The following investigations were carried out:

- (1) The response of the muscle strips to the action of various drugs *in vitro*;
- (2) The response of muscle strips *in vitro* to electrical stimulation at various voltages and duration of stimulation;
- (3) The presence or absence of ganglion cells in all specimens examined by the above methods was checked by ordinary histological means.

Response to Drug Stimulation

Method. Specimens of muscle both longitudinal and transverse were removed at operation from the aganglionic segment of bowel of patients with Hirschsprung's disease and from similar regions of the pelvi-rectal junction and upper rectum from patients with miscellaneous conditions. The mucous membrane was removed and strips of muscle were suspended in oxygenated tyrode at 37° C. The contractions of the muscle were recorded by a lever writing on a smoked drum.

Results. The response of the muscle strips to stimulation by drugs and the effect of various

blocking agents is shown in Tables 1, 2 and 3.

It can be seen that the normal muscle, and the muscle from both the aganglionic segments can all be stimulated by acetylcholine and that this response can be blocked by atropine but not by succinyl choline. Furthermore, muscles from all three sites will respond to nicotine with a contraction, although sometimes this response could only be obtained after the addition of eserine. It was also found that eserine would always increase the amplitude of the contraction with nicotine. The nicotine induced contraction could always be partially or completely blocked by hexamethonium and completely blocked by atropine. These findings hold true for both longitudinal and transverse muscle strips.

TABLE 1
THE RESPONSE OF LONGITUDINAL AND TRANSVERSE NORMAL MUSCLE FROM THE UPPER RECTUM AND COLON TO DRUGS

Stimulating Agent	Response	Blocking Agent		
		Hexame- thonium (2.0 mg.)	Atropine (100 µg.)	Succinyl Choline (2.0 mg.)
Nicotine 400 µg.	+ (2) 0 (1)	B1	B1	0
Eserine 100 µg. + Nicotine 400 µg.	+ Increased res- ponse	B1	B1	0
Acetylcholine 20-50 µg.	+		B1	0
Noradrenaline 100 µg.	0 or fall in base line			
Adrenaline 100 µg.	0 or fall in base line			

50 ml. bath; + = contraction; B1 = block; 0 = no effect
Figures in brackets = number of experiments

TABLE 2
THE RESPONSE OF TRANSVERSE MUSCLE FROM THE AGANGLIONIC SEGMENT OF GUT IN HIRSCHSPRUNG'S DISEASE

Stimulating Agent	Response	Blocking Agent:		
		Hexame- thonium (2.0 mg.)	Atropine (100 µg.)	Succinyl Choline (2.0 mg.)
Nicotine 400 µg.	+ (4) 0 (1)	B1 (2)	B1 (2)	0 (2)
Eserine 100 µg. + Nicotine 400 µg.	+ (5) Increased in all specimens	B1 (3)	B1 (5)	0 (2)
Acetylcholine 20-50 µg.	+ (3)		B1 (3)	0 (2)
Noradrenaline 100 µg.	0 (1) Base line low- ered (3)			
Adrenaline 100 µg.	0 (1) Base line low- ered (3)			
5 Hydroxy trypt- amine	Base line low- ered (1)			

As for Table 1

TABLE 3
THE RESPONSE OF LONGITUDINAL MUSCLE FROM THE AGANGLIONIC SEGMENT OF GUT IN HIRSCHSPRUNG'S DISEASE

Stimulating Agent	Response	Blocking Agent		
		Hexame- thonium (2.0 mg.)	Atropine (100 µg.)	Succinyl Choline (2.0 mg.)
Nicotine 400 µg.	+ (4) 0 (2)	B1 (1)	B1 (2)	0 (2)
Eserine 100 µg. + Nicotine 400 µg.	+ (4) Increased in all specimens	B1 (3)	B1 (2)	0 (1)
Acetylcholine 20-50 µg.	+ (3)		B1 (3)	0 (2)
Noradrenaline 100 µg.	0 (3) Base line low- ered (1)			
Adrenaline 100 µg.	0 (2) Base line low- ered (1)			
5 Hydroxy trypt- amine 100 µg.	0			

As for Table 1

It is widely held that the stimulating action of nicotine is confined to the ganglion cell and that it has no action on either pre- or post-ganglionic nerve fibres or on smooth muscle. In the case of the normal gut, the response is as would be expected, but the contractions of the aganglionic segment from the subjects with Hirschsprung's disease, which could be consistently produced by nicotine, are more difficult to explain. The fact that the nicotine induced contractions could be blocked by atropine and augmented by eserine suggested that the nicotine was stimulating some structure within the colon wall which would release acetyl choline and which was associated with some cholinesterase system.

Response to Electrical Stimulation

In 1955 Paton described a method of stimulating the guinea-pig intestine by means of coaxial electrodes. He concluded that it was possible to distinguish by this method of excitation between pre-ganglionic, post-ganglionic and effector cell structures.

The nature of our specimen obtained at operation made this method of stimulation impossible, but it was considered worthwhile to investigate the nature of their response to electrical stimulation by another method.

Method. The strip of muscle was suspended in oxygenated tyrode at 37° C. Silver electrodes were applied to both ends of the strip and just before stimulation the level of the tyrode was lowered until the muscle and electrodes were completely uncovered. The muscle was then stimulated along its longitudinal axis and the contraction recorded on a revolving smoked drum.

The stimulator provided simple rectangular voltage pulses of variable duration (10 μ sec. to 300 msec.) and amplitude (0 to 200 volts). Its output impedance was 300 ohms. In preliminary experiments the current wave form was observed simultaneously with the voltage wave form by means of a double beam cathode ray oscillograph. It was confirmed that the current wave form was also substantially rectangular except for the usual small spike of relatively short duration (associated with the capacitative component of the impedance between the electrode) at the rising edge of the pulse. The resistance of the electrodes and specimen ranged from 2,000 to 4,000 ohms. For example, for a pulse of amplitude 100 volts the current was of the order of 40 mA. With this longitudinal arrangement of the electrodes a considerable proportion of the total current presumably flows along the moist film over the surface of the specimen and does not contribute to the effective stimulus. The threshold voltage required for stimulation was determined by increasing the amplitude of single pulses in steps until a slight muscular contraction was observed. The tyrode level was then raised and the muscle allowed to rest for five minutes before another determination of threshold for a pulse of longer duration; thus intensity duration curves were constructed.

Results. Fig. 1 shows the intensity duration curve obtained from muscle from the upper rectum. It can be seen that the pattern produced with the longitudinal muscle differs a little from that obtained by stimulating transverse muscle, furthermore, after the muscle is atropinized there is a shift in the curve obtained from transverse muscle but not in that obtained from longitudinal muscle.

Fig. 2 shows the curves obtained in transverse muscle from the aganglionic upper rectum of patients with Hirschsprung's disease and it can be seen that all samples show a shift to the right and are similar to those found in atropinized normal muscle. However, the longitudinal muscle from patients with Hirschsprung's disease is similar to that from normals (Fig. 3).

Discussion

These experiments were undertaken to investigate some of the properties of aganglionic intestinal smooth muscle from subjects with Hirschsprung's disease.

The first group of experiments was concerned with the response of this muscle to various drugs. The response of the aganglionic muscle to nicotine was surprising; all the evidence obtained suggested that a structure was being stimulated which was capable of releasing acetylcholine, but extensive search failed to reveal any ganglion cells. It would appear, therefore, that the stimulating effect of nicotine as far as the intestine was concerned extended beyond the ganglion cells and that other

structures could also be stimulated. Of the nature of these structures it is only possible to speculate, but the tissues which are most obvious or most likely to be concerned are the whorls of non-medullated nerve fibres which appear in the position usually occupied by Auerbach's plexus and it is not unreasonable to suggest that these structures are capable of being stimulated by nicotine to release acetylcholine.

Experiments by Kottagoda (1953) strongly suggest that nicotine is capable of releasing adrenaline-like substances from isolated rabbit ear and that this action can be blocked by hexamethonium. It seems that release of adrenaline from local chromaffin tissue is unimportant here as noradrenaline relaxes rather than contracts this muscle and the augmentation of the response by eserine and its blocking by atropine suggest a cholinergic rather than an adrenergic mechanism.

The hope of clarifying the situation by differentiating between stimulation of muscle and nerve by varying the durations of electrical pulse wave was disappointing. Small difference could be detected between the transverse muscle from the aganglionic segment on the one hand and normal gut on the other. As far as they went they suggested that it was not possible to stimulate the release of acetylcholine by electrical means as in normal intestine, but the differences were very small and the possibility of some form of artefact could not be excluded.

It can therefore be concluded that in the aganglionic segment of gut in Hirschsprung's disease, although there are no ganglion cells present, there are certainly structures which can release acetylcholine when treated with nicotine and cause the intestine to contract.

The most likely site of this acetylcholine release would be the whorls of tissue which appear to replace Auerbach's plexus in the wall of the gut. Whether these structures are capable of playing any part in intestinal activity is not clear, but the presence of some structure which resembles nervous tissue, and which is capable of releasing acetylcholine, may account for the absence of hypersensitivity of the intestine to cholinergic drugs. For to obey Cannon's law of the hypersensitivity of denervated structures the muscle should be truly denervated.

Summary

The response to drugs and electrical stimulation of strips of aganglionic intestine from patients with Hirschsprung's disease has been determined and compared with normal muscle from the same level.

The results show that there is present in the

FIG. 1.—Intensity duration curves of normal transverse and longitudinal muscle from the upper rectum before and after atropine 1 : 500,000.

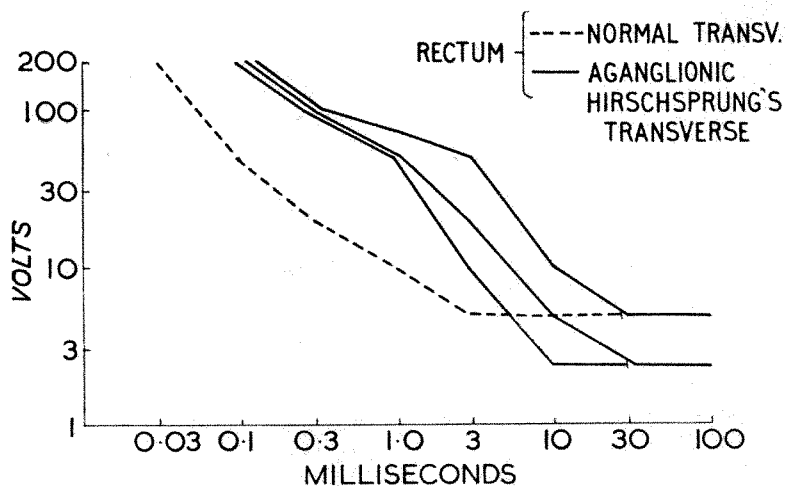
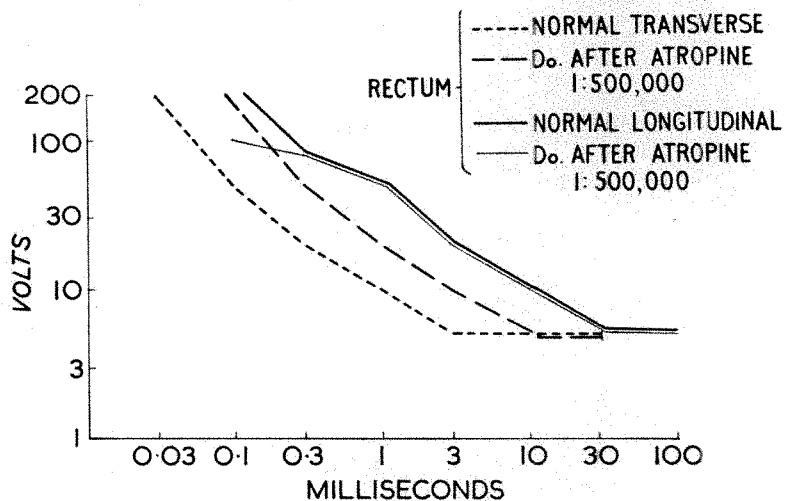
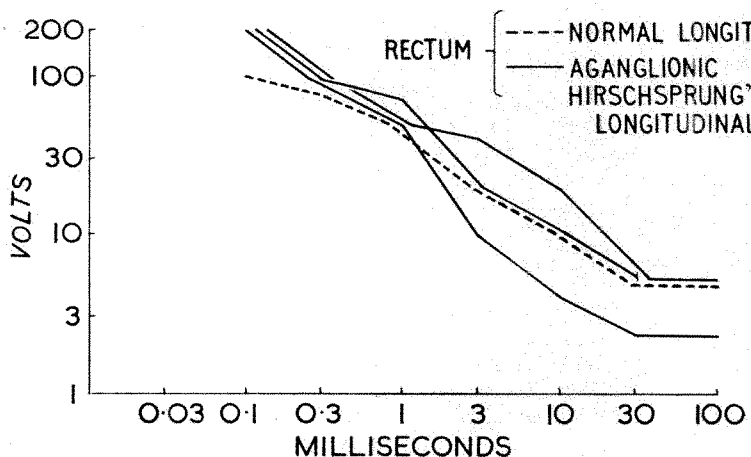


FIG. 2.—Intensity duration curves of transverse aganglionic muscle from the upper rectum of three subjects with Hirschsprung's disease compared with normal muscle.

FIG. 3.—Intensity duration curves of longitudinal aganglionic muscle from the upper rectum of three subjects with Hirschsprung's disease compared with a normal.



aganglionic segment some structure, which on stimulation with nicotine is capable of initiating a contraction mediated by acetylcholine release.

With electrical stimulation, no such acetylcholine release could be demonstrated.

The significance of these results is discussed.

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SPONTANEOUS PERFORATION OF THE COLON IN THE NEWBORN INFANT

BY

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If one excludes those cases of perforation which are secondary to volvulus, intestinal atresia, congenital bands, intussusception, herniation of the bowel, meconium ileus or Hirschsprung's disease, there remains a group of newborn infants who develop perforation of the colon without apparent cause.

Spontaneous perforation of the colon in the neonate was first described by Breslau in 1863. It is a rare event and up until 1939 only 26 case reports could be traced in the medical literature by Thelander.

A number of factors have been considered in the aetiology of spontaneous perforation such as trauma during delivery (Zillner, 1884), congenital defects of the bowel with diverticulum formation (Fischer, 1928), localized vascular insufficiency, and intrauterine or post-partum infection (Thelander, 1939). In 1888 Paltauf reported five cases which he attributed to coprostasis. This aetiological concept has recently received support from the clinico-surgical and pathological studies by Zachary (1957) and Emery (1957) of a group of newborn infants in whom inspissated faecal plugs gave rise to stercoral ulceration with perforation. These authors suggest that the observed faecal impaction may be due to an imbalance between fluid absorption and of propulsion of material along the colon. More recently Haas (1958) has reported a newborn infant with perforation of the transverse colon in whom a haemangiomatic abnormality at the site of perforation was demonstrated.

There still remains a group of newborn infants with one or more perforations of the colon and in whom no clear cut cause can be discovered.

In this paper two further cases of spontaneous perforation of the colon are reported. In one of these, perforation occurred during or immediately after birth and this was associated with marked intraperitoneal haemorrhage. The cause of the

perforation was undetermined. The other child was a premature infant who developed the perforation nine days after delivery and histological examination showed fungal infection at the site of perforation.

Case Reports

Case 1. This female infant was delivered at term as a vertex presentation by a district midwife after an uneventful pregnancy. The child appeared to be vigorous after birth, but abdominal distension with oedema of the vulva was noted. One blood-stained stool was passed after birth and this led to the admission of the child to this hospital.

On examination, six hours after delivery, the child appeared somewhat pale but not greatly distressed. The weight was 5 lb. 5 oz. and the rectal temperature was 95° F. The most striking feature was marked distension of the abdomen. There were prominent dilated veins on the anterior abdominal wall which was oedematous in its lower half. There was also oedema of the vulva. Percussion of the abdomen elicited shifting dullness. A radiograph of the abdomen showed air in the stomach and small bowel. There were no fluid levels indicating obstruction. Examination of venous blood revealed a haemoglobin level of 9.0 g./100 ml.

An abdominal paracentesis at McBurney's point yielded blood-stained fluid with a haemoglobin level of 2.5 g./100 ml. A preoperative diagnosis of rupture of the liver was made and the child was transfused with 100 ml. of group O Rh positive compatible blood. At laparotomy blood-stained fluid escaped from the peritoneal cavity. Floating in this fluid were fragments of fresh meconium (later confirmed histologically). Careful inspection of small and large bowel failed to reveal a perforation. A Meckel's diverticulum was found, but it appeared to be intact. No rupture of the liver was found. The omentum was stained green by the meconium but there was no evidence of peritonitis.

The abdomen was closed again and the child was maintained on intravenous fluid (0.2% saline in 5% invert sugar) while gastric suction was applied. There was no indication of postoperative bleeding, but

48 hours after the operation she suddenly collapsed and died.

At necropsy the peritoneal cavity contained a small quantity of semi-fluid dark brown material. There was some adherence of the bowel loops. A small perforation 3-4 mm. in diameter was found in the region of the hepatic flexure of the ascending colon and a small quantity of meconium was emerging from the perforation. The anatomical position of the bowel at autopsy appeared normal and there was no evidence of volvulus or intussusception. There was thus no obvious cause for the perforation. Other organs showed no abnormalities except for some patches of atelectasis of the lungs.

Histology of sections of the bowel at the site of perforation revealed merely a break in the continuity of the wall with some necrosis of the wall adjacent to the perforation. Ganglion cells were present in normal numbers. The pancreas showed no obvious lesion. The lungs were congested and oedematous.

Case 2. This male infant was born at this hospital weighing 3 lb. The mother developed puerperal sepsis and the infant at 3 days old was transferred to the premature infant unit, his weight then being 2 lb. 11½ oz. Apart from mild icterus, no abnormalities were detected

on clinical examination. He was given feeds of undiluted expressed breast milk from the third day. On the fifth day of life the jaundice had become more intense. The serum bilirubin level was 12 mg./100 ml. Meconium was passed on the fourth and sixth days of life but no stools were noted on the seventh, eighth and ninth days of life. On the ninth day, the infant vomited a feed which was not stained with bile. Some slight distension of the abdomen was noted. A glycerine suppository was prescribed and oral feeding of expressed breast milk was continued. Later in the day two brown watery stools were passed and one of them was blood-stained.

The following day (day 10) the infant continued to vomit and developed gross gaseous distension of the abdomen. The clinical state of hydration was satisfactory. A radiograph of the abdomen revealed the presence of a well-marked pneumoperitoneum (Fig. 1). Gas was present in the small bowel without evidence of fluid levels, and for this reason the site of perforation was thought to be in the colon. Feeds were stopped and intravenous therapy was started with 0.2% saline in 5% invert sugar with the addition of 2.0 g. of potassium chloride to 1,000 ml. of solution. The child was also given 100,000 units of penicillin intramuscularly every eight hours and 50 mg. of streptomycin intramuscularly every 12 hours. On the eleventh day the child's abdomen was still markedly distended and there was oedema of the scrotum. An ill-defined mass could be palpated in the left flank. The infant had also developed oral thrush which was treated with 50,000 units of Nystatin ('mycostatin') every eight hours. On the tenth day the child passed two small scybala. The child's condition continued to deteriorate and death took place on the twelfth day of life.

At necropsy there was marked meconium peritonitis. The peritoneal cavity contained 150 ml. of



FIG. 1.—Radiograph of the abdomen showing a large accumulation of air under the diaphragm and in the right scrotal sac.

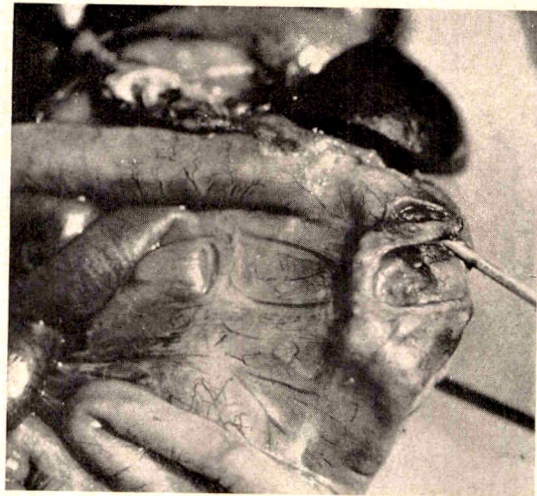


FIG. 2.—Colon with large perforation in anterior wall immediately distal to splenic flexure.

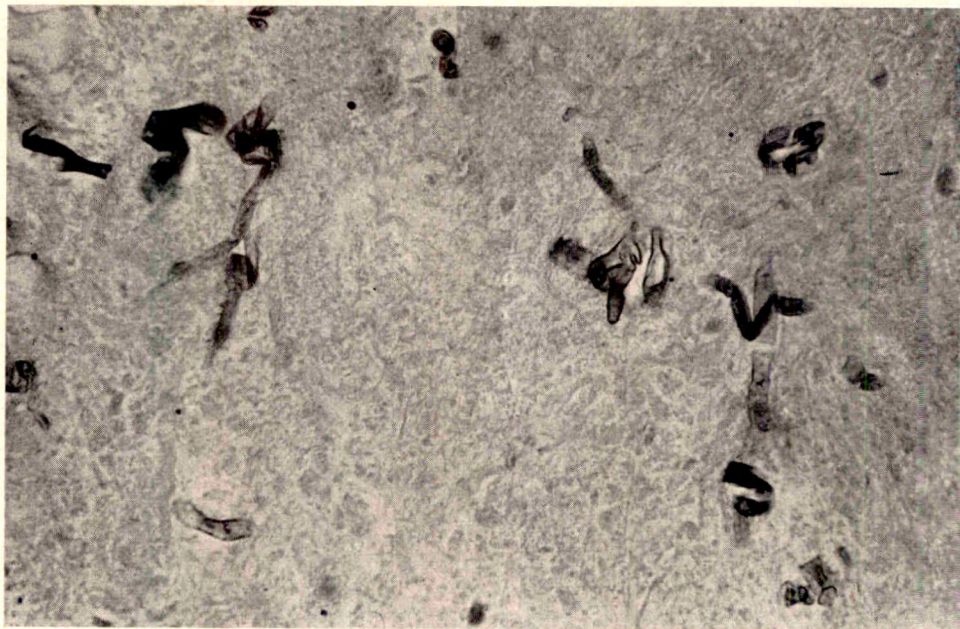


FIG. 3.—Wall of colon adjacent to the perforation showing numerous fungal hyphae.
(Periodic-acid Schiff $\times 480$.)

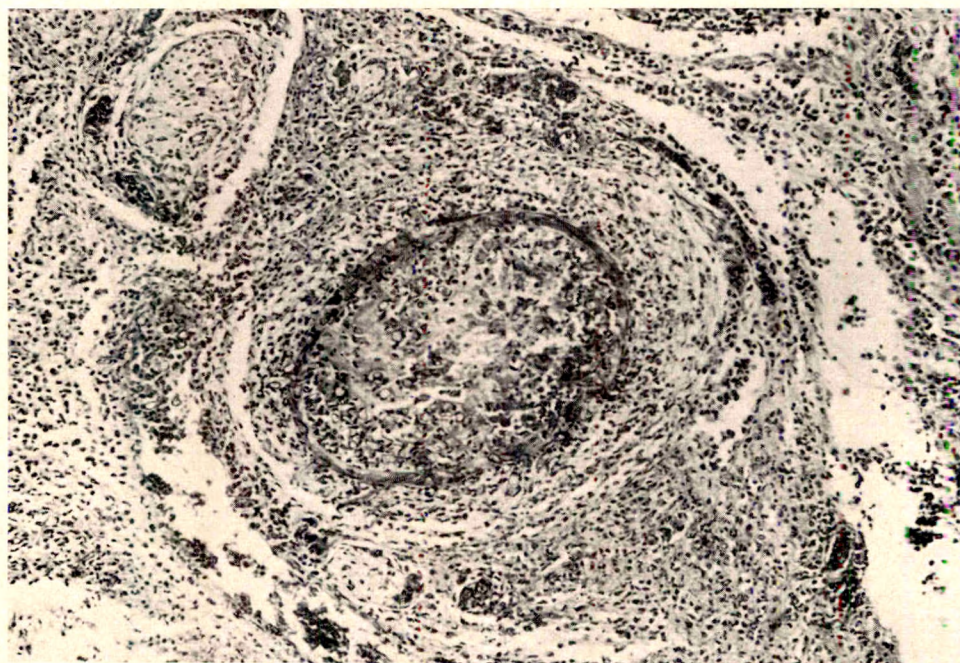


FIG. 4.—Blood vessel in wall of colon adjacent to the perforation showing invasion by inflammatory cells and fungal hyphae.
(Haematoxylin and eosin $\times 150$.)

green purulent fluid. Loops of bowel were densely adherent to the lateral abdominal wall on the left. A large perforation 0.5 cm. in diameter (Fig. 2) was present about 2.5 cm. below the splenic flexure in the anterior wall of the descending colon.

There were still some yellow flecks of inspissated meconium around the perforation and floating in the peritoneal exudate. Anatomically the bowel was normal, and there was no evidence of a volvulus or an intussusception.

Section of the bowel wall at the site of the perforation showed the surrounding mucosa to be necrotic and haemorrhagic. There was haemorrhage into the sub-mucosa and infiltration of the entire wall by polymorphs. The serosa was acutely inflamed and covered by necrotic debris. Fungal hyphae consistent in appearance with the fungus *mucor*, or the related *rhizopus*, were present in the lumen of the bowel, in the wall and in the serosa (Fig. 3). The fungal filaments were large and showed absence of cross-wall formation with free and irregular branching, features suggesting origin from the *mucoraceae*. In many areas the fungi were invading the walls of blood vessels and had come to lie within their lumens (Fig. 4). Unfortunately cultures of the fungus were not made before the tissues were fixed in formalin.

Histology of the pancreas was normal.

Discussion

Our first case presented the clinical picture of intraperitoneal haemorrhage. Hence a preoperative diagnosis was made of rupture of the liver, which is the commonest solid viscus to be damaged in the newborn infant (Stein and Wright, 1953; Arden, 1951; Brown, 1957).

At operation the surprise finding of meconium in the peritoneal cavity, in addition to the blood, indicated perforation of a hollow viscus. The site of perforation was not detected at laparotomy. This difficulty of locating the site of perforation has been encountered by others, and it happened in four of the cases reported by Thelander (1939). Standard (1952) in reporting his case, which was successfully treated surgically, admits that the perforation would not have been visible but for the presence of leaking barium suspension which he had given to the infant. In a case reported by Franklin and Hosford (1952), the perforation was only found at the second operation.

Necropsy in our first case failed to reveal a cause for the perforation, but it must be admitted that a close study of the blood supply to the affected segment of bowel was not carried out. The clinical and experimental studies of Louw and Barnard (1955) have indicated that vascular occlusion plays an important role in the production of intestinal

atresia in the newborn infant. Their work may have some application in the elucidation of the aetiology of spontaneous perforation of the colon. We suggest that, in future, a careful study be made of the blood supply to the area of a spontaneous perforation of the colon. We have assumed that the intraperitoneal bleeding in our case arose from the same site as the perforation, but this was not obvious at autopsy, the bleeding having ceased post-operatively.

Case 2 is of interest in that this premature infant was progressing satisfactorily until the ninth day of life. The child was starting to regain its post-natal weight loss, when it failed to pass stools for three successive days. As in Case 1 there was the passage of one blood-stained stool and it is possible that this finding in the presence of abdominal distension may be of help in the diagnosis of spontaneous perforation of the bowel.

Three possibilities suggest themselves as to the cause of the perforation in Case 2. Firstly this perforation could have followed on stercoral ulceration caused by inspissated meconium. The passage of two small hard pieces of faeces and the finding of residual thickened meconium at necropsy are in favour of this suggestion. However, we were unable to analyse the water content of the meconium as was done by Emery (1957).

Secondly the perforation may be aetiologically connected with the finding of *mucor* (or *rhizopus*) in the bowel wall at the site of perforation. *Mucor* has been found in association with perforation in other parts of the gastro-intestinal tract. Moore, Anderson and Everett (1949) described a widespread ulcerative colitis in a non-diabetic female aged 37 years caused by *mucor* which resulted in death after perforation and generalized peritonitis. Watson (1957) reported perforation of the stomach in association with *mucormycosis* in a child of 26 months suffering from malnutrition. A similar perforation was described by Gatling (1959) in a 4-day-old neonate. Thus this fungal infection may have been the primary cause of the perforation in Case 2. It is also possible that the fungus aggravated a perforation caused initially by hardened meconium.

Until recently the prognosis of spontaneous perforation was thought to be uniformly hopeless. However, in 1952, Standard, in America, and Franklin and Hosford, in Britain, reported survivals following surgical repair. Thus laparotomy is probably advisable whenever the condition of the patient permits. Preliminary decompression of the abdomen may be necessary to increase vital capacity (Standard, 1952).

Summary

Two cases of spontaneous perforation of the colon are reported, one in a full term and the other in a premature infant. There was an associated intraperitoneal haemorrhage in Case 1, and in this infant no demonstrable cause was found for the perforation.

In the second baby the perforation was found in association with inspissated meconium and the presence of fungal infection in the bowel wall morphologically either mucor or rhizopus. Unfortunately cultures of the organisms were not taken.

Our thanks are due to Dr. I. Frack, Superintendent, Baragwanath Hospital, for permission to publish these cases, Dr. E. Kahn, Senior Paediatrician, for criticism and advice, the Director of the South African Institute for Medical Research, for facilities granted, and Mr. M. Ulrich for the photographs.

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THE PROGNOSIS IN IDIOPATHIC HYPERCALCAEMIA OF INFANTS

BY

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Two distinct types of idiopathic hypercalcaemia of infants have been recognized; a mild or simple type, in which recovery is said to be complete, and a severe type, which results in death or physical and mental retardation (Lightwood and Stapleton, 1953; Lowe, Henderson, Park and McGreal, 1954). Although most cases conform to one or other type, it has recently become apparent that the distinction is not a clear one, and that cases with features of both types may occur (Russell and Young, 1954; Rhaney and Mitchell, 1956; Joseph and Parrott, 1958). Moreover, a few of the supposedly mild cases have died and autopsy has disclosed nephrocalcinosis, affecting mainly the medulla of the kidney (Rhaney and Mitchell, 1956). Hence it is of some importance to determine whether infants with the simple type who recover clinically sustain any permanent renal damage.

The severe form of idiopathic hypercalcaemia is accompanied by considerable dwarfing (Schlesinger, Butler and Black, 1956; Fellers and Schwartz, 1958), while infants with the simple type show retardation of growth during the acute phase of the illness and often for some time thereafter (Creery and Neill, 1954). It is therefore of interest to know how long this retardation persists after the biochemical disturbance has been corrected.

No full follow-up study has yet been reported although Forfar, Balf, Maxwell and Tompsett (1956) gave some details of four cases followed for one to three years; Creery and Neill (1954) briefly described the progress of their patients up to 18 months after the illness, and there have been reports on single cases (Bonham Carter, Dent, Fowler and Harper, 1955; Smith, Blizzard and Harrison, 1959). With a view to obtaining more detailed information about the prognosis, the progress of all children with the simple type of idiopathic hypercalcaemia seen in Dundee during a period of four years has been followed.

Details of the follow-up study

From 1953 to 1956 inclusive, 18 infants were diagnosed as having the simple type of idiopathic

hypercalcaemia. The principal clinical features of the group have been briefly reviewed elsewhere (Mitchell, 1958) and detailed case histories have been recorded for eight of the infants; Cases 2, 3, 4 and 6 by Lowe *et al.* (1954); Cases 1 and 2 by Morgan, Mitchell, Stowers and Thomson (1956); and Cases 1 and 3 by Rhaney and Mitchell (1956). In Dundee the criterion now accepted for the diagnosis of hypercalcaemia in infants is a level of plasma calcium above 12.0 mg. per 100 ml. measured on two separate occasions, using an oxalate-permanganate method for the determination of calcium. During the four-year period, at least five other infants were believed to have idiopathic hypercalcaemia of the simple type (two were included in the report by Lowe and his colleagues in 1954 as Cases 5 and 7), but the above criterion was not fulfilled and they are not included in the group. Of the 18 infants in whom the diagnosis was regarded as established, four died and three of these were studied at necropsy (Rhaney and Mitchell, 1956). The 14 survivors are the subject of this report.

Tests of renal function were carried out on all children who had shown any evidence of possible renal involvement during the original illness, i.e. all those whose urine contained leucocytes at any time during the illness or who had had a level of blood urea over 50 mg. per 100 ml. on any occasion. The tests were made at least once between two and five years after the onset of symptoms.

Since the children had endured much investigation and treatment in the past, and most were in the pre-school age group when clinical investigation is most difficult, it was considered desirable to limit the study to the minimum required to provide a reasonable estimate of kidney function. Thus tubular function was assessed by the ability to concentrate and acidify the urine and glomerular function by the clearance of creatinine. Since the determination of creatinine clearance by methods which also measure non-creatinine chromogen is not satisfactory (Doxiadis and Goldfinch, 1952; Barnett and

Vesterdal, 1953), specific endogenous creatinine was measured by Hare's method (1950) using a Unicam SP600 spectrophotometer. Two timed collection periods of between one and two hours were used and the results were expressed in terms of surface area calculated from the Dubois nomogram. Urea clearance was also estimated but in most cases the rate of urine secretion was not adequate for maximum clearance of urea to be determined.

The children were examined at intervals to assess their growth and development and to determine how long the biochemical disorder persisted. Although some of the children had gone abroad or to distant parts of the country it was possible to pursue these investigations more or less completely in all but one of the 14. This child (Case 14) was admitted to hospital at the age of 4 months with characteristic symptoms, a plasma calcium level of 13.5 mg. per 100 ml., blood urea level of 26 mg. per 100 ml., and no abnormality of the urine. He was treated with a low-calcium milk preparation and the plasma calcium level had returned to normal by the age of 6 months. At 8 months he weighed 16 lb. 5 oz. (7.4 kg.); he was not seen again because his family were nomadic tinkers and could not be traced.

Results

General progress. Three to six years after the onset of idiopathic hypercalcaemia, all 13 children were in good health. They were taking a full mixed diet except for one who was a vegetarian from choice. None was taking cod liver oil or additional vitamin D except that in patent cereal foods. Two of the mothers stated that their children were still slightly constipated, otherwise none of them had any complaints. Some of the children had sat up and walked at the usual times but most had been slightly delayed. Nevertheless, all were sitting up without support by 12 months, and all had taken the first unaided step by 21 months. Intelligence was not formally tested but ordinary clinical observation indicated that all the children except one were well up to average mental development for their ages. The one exception (Case 1) showed slight mental retardation at the age of 5½ years. However, although there had never been radiological abnormalities of her skull, she did have some of the facial characteristics described in the severe type of idiopathic hypercalcaemia (Joseph and Parrott, 1958), namely, a squint, slight epicanthic folds and a prominent upper lip, and thus possibly represented an intermediate form between simple and severe types.

Cardiovascular system. Three children who had had cardiac murmurs during the acute illness had

no detectable cardiac abnormality at the most recent examination. Two of the three had originally had T wave abnormalities in the electrocardiogram and these also had disappeared. In none of the 13 children was the blood pressure more than 110/80 mm. Hg at review.

Biochemical investigations. All the children had normal levels of plasma calcium at the last recording (range 9.0-11.1 mg. per 100 ml.). Because the level of plasma calcium was determined at irregular intervals in some of the early cases, it was not always possible to be certain exactly when the hypercalcaemia subsided, but the minimum duration was assessed as the time interval between the first diagnosis of hypercalcaemia and the last occasion on which a level of above 12.0 mg. per 100 ml. was recorded; the Table shows the minimum duration of hypercalcaemia in each case. During the original illness, the plasma alkaline phosphatase level was known to be less than 10 King-Armstrong units in seven of the 13 children; all seven had levels above 10 King-Armstrong units at the latest review. Raised plasma cholesterol levels (over 280 mg. per 100 ml.) had been recorded in three of the 13 children but in all three the cholesterol level was less than 230 mg. per 100 ml. at review.

Renal function. In none of the 13 cases did the urine contain protein, sugar or abnormal numbers of cells at the time of review. Tests of renal function were made on the 10 children who had shown evidence of possible renal involvement during the original illness and the results are shown in the Table. In the other three children only concentrating and acidifying abilities were tested. The ages of the children at the time of these tests ranged from 2 years and 5 months to 5 years and 9 months. All the children except one concentrated the urine to a specific gravity of 1.025 or more when fluids were withheld for 12 hours. The one exception (Case 2) concentrated to 1.023; no opportunity arose to repeat the test on this child. All the children were able to acidify the urine to pH 5.2 or less, measured with universal indicator and narrow range indicator papers (B.D.H.). In five of the children it was necessary to give ammonium chloride by mouth in a dose of 0.1 g. per kg. of body weight in order to demonstrate this acidifying ability.

The creatinine clearance was more than 75 ml. per min. per 1.73 m.² of surface area in seven of the 10 children tested, while in three it was between 60 and 75. In two of these three (Cases 8 and 12), however, the creatinine determinations were done in a different laboratory, and total Jaffé chromogens

were measured instead of specific endogenous creatinine. The results would thus be expected to be falsely depressed (Roscoe, 1958) and unfortunately the tests could not be repeated in these two children using Hare's method (1950). However, the maximum and standard clearances in Case 12, and the standard urea clearance in Case 8, were all more than 100% of average normal, and it is likely that the true creatinine clearance was considerably higher. One child (Case 4) with a clearance of specific endogenous creatinine of 65.5 ml. per min. per 1.73 m.² was aged 3½ years at the time of the test. There are no satisfactory standards of normal for children of this age, and the clearance value, though low, cannot be regarded as necessarily abnormal, especially as a simultaneous urea clearance test indicated a standard clearance of 117% of average normal.

The standard urea clearance was over 100% of average normal in nine of the 10 children; in three (Cases 2, 11 and 12) the maximum clearance of urea was also determined, each value being above 100% of average normal. The only child with a low standard urea clearance (58% of average normal) was the one suspected of having a form of idiopathic hypercalcaemia intermediate between the simple and severe types, but since the other tests were satisfactory (see Table), this rather low value is of dubious significance.

Growth progress. The heights and weights of the 13 children were measured at intervals throughout the follow-up period, and these, together with measurements made during the illness and any recorded by the mother before admission to hospital, have been plotted on height and weight charts (Figs. 1 and 2). The standards used for these charts are

derived from the Oxford Child Health Survey (Acheson, Kemp and Parfit, 1955) and standard deviations (S.D.) from the mean values are shown because only these were published. The -2 and -1 S.D. lines correspond to about the 2.25th and 16th percentiles respectively, and the +1 and +2 S.D. lines to about the 84th and 97.75th percentiles, the error due to the asymmetry of the distribution curve for weight being quite small (Polani, 1959). When weighed, the children were naked or wearing underpants, and height was measured in the standing position (in children over 18 months of age).

Nearly every weight chart shows clearly the deviation of the weight curve during the first two years of life caused by the hypercalcaemic episode and the subsequent return to the original channel. The data on heights are fewer in number and no clear effect on height is demonstrated. In no case is either the height curve or the weight curve still pursuing a course outside the -2 S.D. line. In two cases the height curves are between the -2 and -1 S.D. lines, and in one other case the weight curve is between the -2 and -1 S.D. lines.

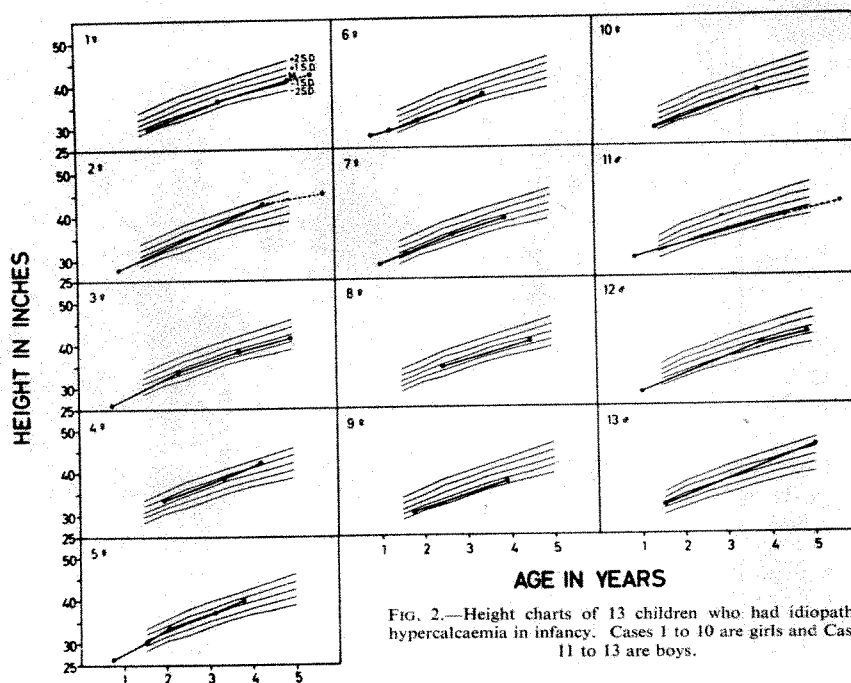
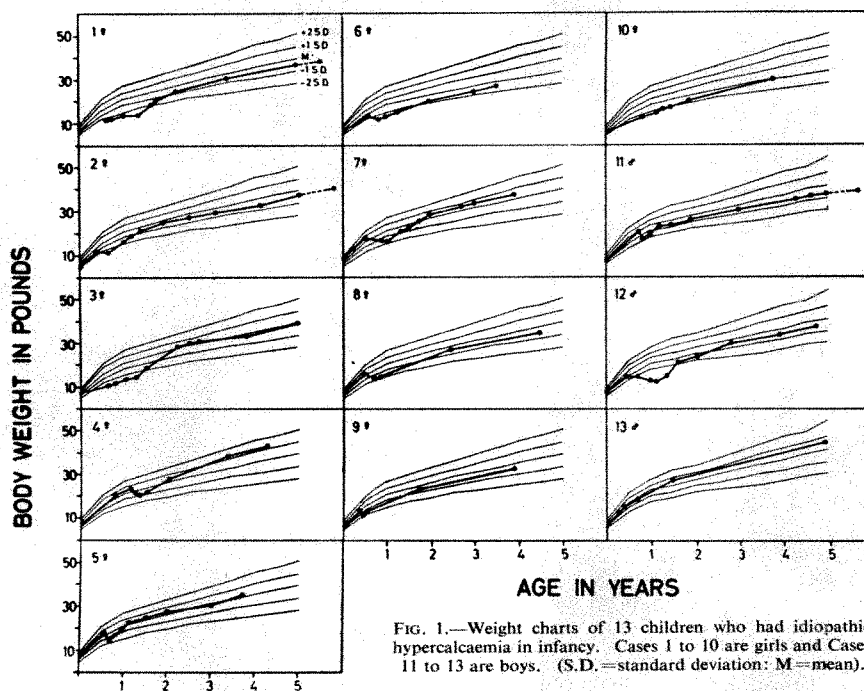
Discussion

The tests of renal function did not reveal any significant abnormality in this group of children two to five years after the onset of idiopathic hypercalcaemia. Thus, the ability to concentrate and acidify the urine satisfactorily showed that tubular function was unimpaired. The inulin clearance test, which is generally regarded as a valid measure of glomerular filtration rate, is not easily applicable to young children, and so the clearance of specific endogenous creatinine was used when possible as an indication of glomerular function. This would

TABLE

SUMMARY OF BIOCHEMICAL FINDINGS AND RENAL FUNCTION TESTS IN 14 CASES OF IDIOPATHIC HYPERCALCAEMIA

Case No.	Sex	Maximum Level of Calcium in Plasma (mg./100ml.)	Minimum Duration of Hypercalcaemia (> 12.0 mg./100 ml.)	Maximum Level of Urea in Blood (mg./100ml.)	Minimum Duration of Uraemia (> 50 mg./100 ml.)	Tests of Renal Function			
						Time in Years Between Onset and Tests	Creatinine Clearance (ml./min./1.73 m. ²)	Minimum pH of Urine	Maximum S.G. of Urine
1	F	16.8	5 months	135	7 months	5	103.9	<5.0	1.028
2	F	14.0	28 months	58	2 weeks	4	115.5	<5.0	1.023
3	F	13.9	3 months	76	4 weeks	3½	78.9	<5.0	1.030
4	F	13.0	2 weeks	48	nil	3	65.5	5.2	1.028
5	F	15.1	1 week	46	nil	2½	99.9	<5.0	1.030
6	F	16.1	4 weeks	60	2 weeks	2½	98.2	5.0	1.026
7	F	19.0	2 weeks	63	2 weeks	2½	77.3	<5.0	1.025
8	F	16.0	3 weeks	60	1 week	2	64.6	5.0	1.027
9	F	13.4	2 weeks	29	nil	3½	—	<5.0	1.029
10	F	13.3	1 week	37	nil	3½	—	5.2	1.025
11	M	15.6	3 months	40	nil	5	103.9	<5.0	1.028
12	M	13.3	8 months	72	8 months	4½	62.3	5.0	1.025
13	M	14.0	4 weeks	50	nil	5	—	<5.0	1.025
14	M	13.5	2 weeks	50	nil	—	—	—	—



be valid in children with disease affecting the renal tubules (Mattar, Barnett, McNamara and Lauson, 1952), but the evidence indicated that all these children had normal tubular function, and the creatinine clearance was therefore accepted as an approximate measure of glomerular filtration. The values obtained are somewhat lower than those recorded by Ikkos and Ström (1955) for older children, but all fall within a fairly small range and are considered to indicate satisfactory glomerular function.

It is well established that persistent hypercalcaemia can cause renal damage, calculus formation and calcification (Thomas, Connor and Morgan, 1959) and it is therefore remarkable that one child (Case 2), who was known to have had hypercalcaemia for at least 28 months, should have apparently completely normal renal function at the age of 4½ years. In the earliest patients, who were treated by withdrawal of vitamin D alone, the hypercalcaemia was allowed to persist much longer than in the later ones, in whom active measures were taken to reduce the level of plasma calcium. Low calcium diets alone were not always successful in reducing the level promptly but a rapid fall usually followed the administration of cortisone, and this action was sometimes used to maintain the plasma calcium at a lower level until the reduction in calcium intake could become effective.

The way in which cortisone acts is not understood, although its beneficial effect in idiopathic hypercalcaemia of infants may in part be due to reduced absorption of calcium from the intestine (Anderson, Dent, Harper and Philpot, 1954; Morgan *et al.*, 1956). In an attempt to throw further light on the mode of action of cortisone, the level of plasma calcium was measured in four untreated hypercalcaemic infants before, and at short intervals after, a single oral dose of cortisone (Fig. 3). The rate of fall in the plasma calcium level indicates that some mechanism more rapid than the intestinal action must be operating initially. This cannot be a renal tubular effect, since there was no increase in calcium in the urine during these tests. It has been postulated by Cruickshank and Kodicek (1958) that cortisone acts by influencing the metabolism of skeletal tissues and there is indirect evidence that cortisone can inhibit the resorption of bone (Thomas and Morgan, 1958; Morgan, 1959).

The charts for height and weight indicate satisfactory growth progress during the years immediately following clinical recovery from the simple type of idiopathic hypercalcaemia. There is no apparent association between the rate of return to the expected growth channel and the duration or degree of either

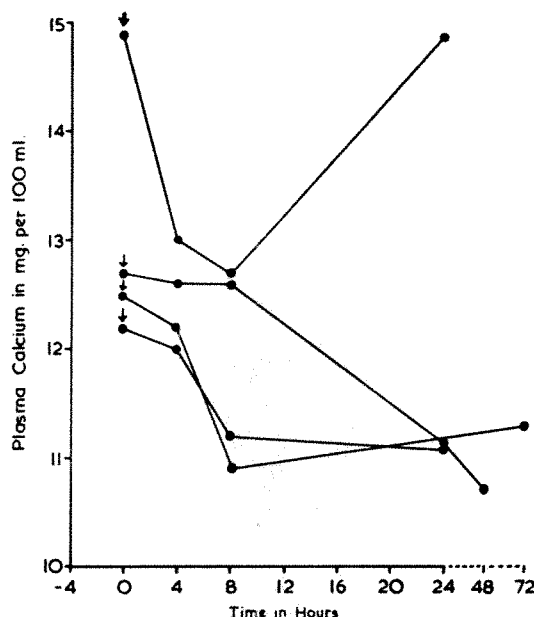


FIG. 3.—The effect of cortisone on the plasma calcium level in four cases of idiopathic hypercalcaemia. (The arrow indicates 25 mg. cortisone acetate given orally.)

the hypercalcaemia or the elevation of blood urea. Thus the child who was known to have had hypercalcaemia for at least 28 months (Case 2) was above average in height. Her weight curve did pursue a course below the mean level, but this was probably not attributable to the prolonged metabolic disturbance, since height as well as weight has usually been affected by persistent elevation of plasma calcium in cases of the severe type of idiopathic hypercalcaemia, as it was also in the patient described by Smith *et al.* (1959), who seems to have had the simple type of idiopathic hypercalcaemia.

This investigation provides evidence in support of the opinions of earlier workers that recovery from the simple type of idiopathic hypercalcaemia is usually complete. Nevertheless, the possibility of unexpected death in the acute stage (Rhaney and Mitchell, 1956), the recognition of cases intermediate between simple and severe forms of idiopathic hypercalcaemia, and the prolonged course occasionally followed by apparently simple cases (Smith *et al.*, 1959), should make one hesitate to give an unreservedly good prognosis for the individual child.

Summary

Thirteen cases of the simple type of idiopathic hypercalcaemia of infants have been followed up

for three to six years after the onset of the illness.

All the children are in good health and all except one are mentally normal, the one exception having certain features suggesting a syndrome intermediate between the simple and severe types.

In all cases the abnormal biochemical findings originally present have disappeared. Simple tests of renal function performed two to five years after the onset did not indicate any residual impairment of renal function.

Although the hypercalcaemic episode caused a marked deviation of the weight curve in nearly every child, the height and weight charts indicate that subsequent progress has been satisfactory.

I wish to thank Professor J. L. Henderson and Dr. James Thomson for permission to include their cases in this study and for their kindly criticism. I am very grateful to Dr. F. L. Mitchell and Dr. H. G. Morgan for the biochemical investigations and for helpful advice. I also thank Miss M. W. Mackenzie for the illustrations.

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PNEUMOMEDIASTINUM AND SUBCUTANEOUS EMPHYSEMA IN STATUS ASTHMATICUS, REQUIRING SURGICAL DECOMPRESSION

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 10, 1959)

Leakage of air into the interstitial tissues of the lungs of sufficient degree to produce pneumomediastinum and subcutaneous emphysema is an uncommon and potentially fatal complication of bronchial asthma in childhood. Another possibly fatal complication of similar causation is tension pneumothorax. It is possible that interstitial emphysema occurs more frequently in severe asthma and allied states than our usual methods of diagnosis allow us to discover, producing additional interference with ventilation by distending and splinting the area of lung involved. This case report and discussion of some relevant literature may serve to illustrate some of these points.

Case Report

A boy, 8 years of age, had had periodic attacks of asthma for four years, some precipitated by hay making and others by dusting of rooms. He had been admitted to this hospital in November, 1956, on the third day of a severe attack in which there was blood staining of the sputum; the attack responded to intravenous aminophylline and oral ephedrine hydrochloride. Skin tests with Benedicts reagents showed marked sensitivity to mixed pollens, house dust, horse hair and cat fur. Between January and March, 1957, hyposensitization with a mixed vaccine was attempted, one brief asthmatic attack occurring during the course. A paternal uncle and a grand-uncle were asthmatic.

The present attack had commenced some 20 hours before his admission on April 14, 1957; he had been given approximately 12 subcutaneous injections of adrenalina by his family doctor and a final injection of 0.5 ml. in divided doses by the physician in a district hospital; some ephedrine had been given orally. He had to be brought from an island off the west coast by boat and then 60 miles by road to this hospital. On admission there was marked expiratory and inspiratory dyspnoea, with inspiratory lower costal retraction; the respiratory rate was 55/min., the cardiac rate 160 and the temperature 100° F. There appeared to be acute-on-chronic pulmonary emphysema and the cardiac

dullness was obliterated. The blood pressure was 140/90 mm. Hg, the weight 49 lb. Small amounts of blood-stained sputum were expectorated with difficulty and cough was forcible and distressing. Aminophylline 0.125 g. was given intravenously on two occasions with temporary relief; 500,000 units of intramuscular penicillin and $\frac{1}{2}$ gr. of phenobarbitone were given, and repeated at 12 hour and six hour intervals respectively.

Four hours after admission subcutaneous emphysema was observed above the clavicles, quickly spreading to the neck, cheeks and axillae; the blood pressure was then 150/90 mm. Hg. Three hours later the respiratory distress became more marked and was accompanied by cyanosis despite an efficient oxygen tent. The chest was almost fixed in the maximal inspiratory position, the neck and upper thoracic veins were engorged, the pulse volume was diminished and showed paradoxical respiratory variation.

Cortisone acetate 100 mg. was given intramuscularly. Pneumomediastinum was suspected and confirmed by portable radiographs (Figs. 1 and 2). As the boy's condition was critical, horizontal incisions of about 1½ in. were made under local anaesthesia above each clavicle, about eight and a half hours after admission. Exploration with sinus forceps through the incisions allowed release of air under pressure with marked relief of the distress and of the venous distension. The pulse volume improved and the boy rested comfortably. Gradual resolution of the asthmatic attack followed, the subcutaneous emphysema taking some days to disappear; several exacerbations of the asthma occurred before his discharge nine weeks later. The boy has since been admitted with two severe attacks without recurrence of any observable pulmonary air leak.

Discussion

Peterson (1947) states that mediastinal emphysema was first described by Müller in 1888, while Matts (1957) states that Laennec (1827) described it under the name of 'interlobular emphysema'.

Macklin and Macklin (1944) discuss the subject of non-surgical interstitial emphysema of the lungs and mediastinum exhaustively, and they maintain

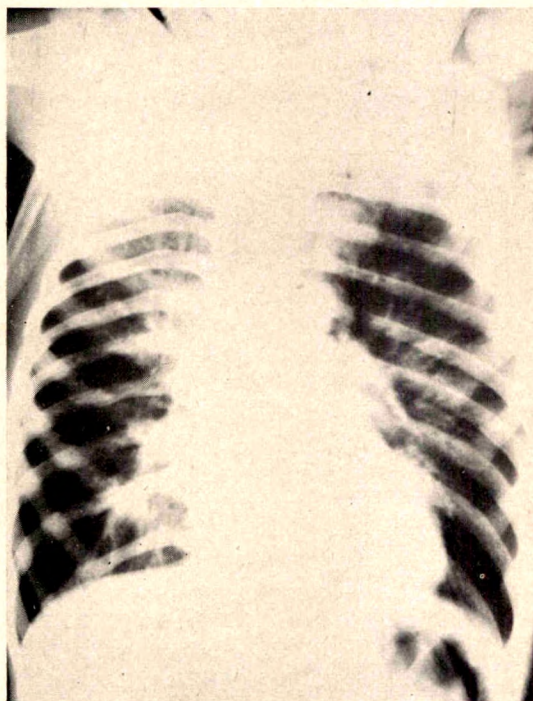


FIG. 1.—Portable antero-posterior film of chest showing distension of lungs, some infiltration of both upper lobes, mainly right, a translucent ring of air surrounding the aortic knuckle and air bubbles in left axilla.

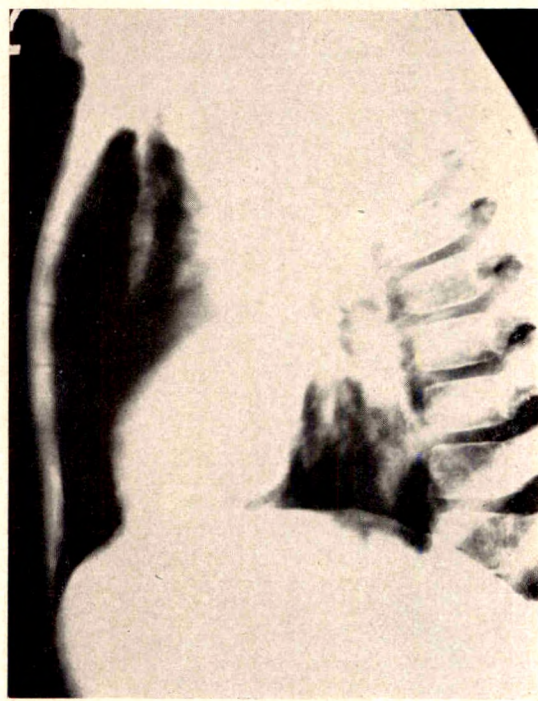


FIG. 2.—Portable lateral film of chest showing large volume of air trapped between heart and sternum, outlining what is probably the thymus. The contrast between the small (presumably compressed) heart and the distended thorax is striking.

that the basic requirement for alveolar rupture and leakage of air into the interstitial tissues of the lung is a pressure gradient from the alveoli to the perivascular sheaths. The pressure gradient may arise from over-inflation of the lung or lowering of vascular pressure; an example of the former, would be compensatory over-inflation of the lung surrounding an area of atelectasis, and of the latter, would be pulmonary embolism. In the majority of instances of interstitial emphysema there is also an increase in the alveolar pressure. Over-inflation of lung may be localized, as in the lung adjoining an atelectatic area or in lung distal to a ball valve bronchial obstruction. Generalized over-inflation appears to cause most cases of air leak, the most common examples being severe expiratory dyspnoea as in bronchial asthma, forceful coughing, severe straining as in lifting of heavy weights or during labour, other examples being forceful resuscitation of the newborn infant or anaesthetized patient. Other examples of interstitial emphysema in which various factors operate and may combine are neonatal atelectasis, obstructive laryngitis, tracheotomy, pertussis, bronchial foreign bodies,

severe exercise, lung blast and caisson disease. Pulmonary infection appears to be a factor in many cases, presumably by weakening the alveolar wall, and combined with forceful cough is probably the cause of interstitial emphysema in influenza and measles.

Once air has leaked from the alveolus, if the pressure gradient is maintained, as by persistent dyspnoea and/or coughing, the air usually tracks centrally along the vascular sheaths to the lung root and mediastinum, as Macklin and Macklin (1944) have shown both by experiment and in autopsy material; it may also track peripherally to the subpleural space. The interstitial emphysema may both distend the lung, reducing its mobility and thus interfering with ventilation, and interfere with the pulmonary circulation by compressing blood vessels. When air reaches the mediastinum in large quantities, and does not readily find egress, a tension pneumomediastinum is produced, which impedes venous filling of the heart and thus further restricts the pulmonary, as well as the systemic, circulation; marked venous distension of the neck, head and trunk will occur. Electrocardiographic changes

have been reported (Master, Kalter and Dack, 1941). To these effects will, in many cases, be added interference with ventilation by local or generalized alveolar emphysema and later by pulmonary infection.

From the mediastinum air may escape into one or both pleural cavities, into the tissues of the neck and thence to the head and trunk, or into the retroperitoneal space from which it may rupture into the peritoneum; escape of air by one or other of these routes usually acts as a safety valve, preventing cardiac tamponade, although the other hazard of tension pneumothorax may be produced. Macklin and Macklin (1944) believe that varying degrees of interstitial emphysema may frequently occur in such conditions as severe asthma and may play a significant part in the dyspnoea; although agreeing with other authors that such leakage of air is usually benign, due either to its limited extent or to the operation of the 'safety valve', they emphasize its potentially fatal nature.

Norman (1957) in describing a boy of 21 months who had a pneumothorax and subcutaneous emphysema complicating bronchial asthma on two occasions, found 30 published cases of subcutaneous emphysema in asthma. Two were fatal, and in two others incision of the skin in the neck to allow escape of air was necessary. Macklin and Macklin (1944) cite reports of other fatal cases of asthma where death was attributable to pneumomediastinum, pneumothorax, or both, in the absence of subcutaneous emphysema.

Recognition and Management. Macklin and Macklin (1944) maintain that the presence of subcutaneous emphysema in the neck presupposes a pneumomediastinum, which should also be suspected in severe asthma without subcutaneous emphysema if there is marked venous distension of the neck, head and upper thorax, or other evidence of cardiac tamponade such as paradoxical pulse with falling blood pressure. In patients old enough to complain, there may be substernal pain of anginal nature, abdominal pain, or a feeling of fullness in the upper chest and neck. Obliteration of cardiac dullness, bulging and tympany of the upper sternum are signs of pneumomediastinum but will be more commonly due to acute generalized pulmonary alveolar emphysema. Systolic crunching or crackling sounds, best heard with the patient in the left lateral position (Hamman, 1937) are said to be diagnostic of air in the mediastinum. Lateral radiograph of the chest is the most valuable procedure, the presence of air between the cardiac and sternal shadows being diagnostic; air may also be

seen surrounding the heart in postero-anterior views. Increasing cyanosis and signs of reduced cardiac output, with weakening peripheral circulation will call for urgent decompression of the trapped air in the mediastinum. If air is confined to the mediastinum, needling and under water drainage are indicated. When subcutaneous emphysema is present, incision of the skin in the suprasternal notch is usually adequate, exploration with sinus forceps or gloved finger being continued until sufficient air has been released. Schrire and Schrire (1952) described a 6 in. horizontal incision in the suprasternal notch, vertical incision of the platysma, elevation of the thyroid and insertion of a finger down either side of the trachea to facilitate escape of air, but this procedure should hardly be necessary in most cases. Bilateral incisions, as in the present case, would not seem to be necessary. Following decompression, the wound should be left open and covered with loose gauze, broad spectrum antibiotic cover being provided.

Summary

Pneumomediastinum and subcutaneous emphysema complicating severe asthma in an 8-year-old boy are described; release of air by means of incisions of the skin in the neck was necessary due to signs of cardiac tamponade.

Some of the relevant literature is reviewed, including an acceptable theory of production of emphysema of interstitial pulmonary tissues, mediastinum and subcutis.

Recognition and management of pneumomediastinum are briefly discussed.

I wish to thank Mr. D. Kneafsey for reading and criticizing this paper and for his help with later interpretation of the radiographs; also Dr. John Horan for his case notes and help with management of the patient.

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Addendum

A 4-year-old girl was admitted in March, 1960, in the third day of an attack of bronchopneumonia, with subcutaneous emphysema in the neck of six hours' duration. Within a few hours the emphysema had spread to the cheeks, left temple and left lower eyelid, both axillae, and had formed a tense V-shaped swelling over the upper chest with its apex at the sternal angle. There was a forceful dry cough with some expiratory difficulty, wheezing and grunting, suggesting predominant involvement of the bronchioles. Pneumomediastinum was shown by many crunching and bubbling sounds with respiration over the whole sternal area and by very well marked praecordial systolic 'crunching' sounds; the pneumomediastinum was confirmed by radiography. The child was not very distressed at any stage and there was no overfilling of neck veins, but there was thought to be some diminution of pulse volume during inspiration. An interesting finding was regular lowering of the amplitude of the ventricular complexes in the E.C.G. during inspiration, this being most marked in leads V_1 and V_4R , without any other abnormal finding. The cardiac rate averaged 150 per minute for the first few hours, and no fall in blood pressure occurred. It is

presumed that the E.C.G. findings were due to compression of heart or great vessels, as they had become less marked some days later, and had gone two weeks later.

It was not necessary to decompress the emphysema and this had almost completely disappeared five days later. The respiratory infection responded satisfactorily, intramuscular penicillin being given for eight days. Radiographs showed some pulmonary distension and slight infiltration consistent with a diffuse bronchopneumonia, in addition to air bubbles in soft tissue and mediastinum.

A further interesting feature in connexion with this case is that her brother was admitted to the Fever Department of this hospital in November, 1954, when aged 5 years (under the care of Dr. B. J. O'Driscoll) with subcutaneous and mediastinal emphysema complicating measles bronchopneumonia, the condition subsiding uneventfully with penicillin treatment. The occurrence in siblings of pulmonary air leakage complicating respiratory infections might be due to a common developmental anomaly of the lungs predisposing towards air leakage with certain types of respiratory involvement. It might equally well be coincidental.

CREATINURIA IN MÖBIUS' SYNDROME

BY

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(RECEIVED FOR PUBLICATION OCTOBER 19, 1959)

Since the first description by Harlan (1881) of a patient with bilateral congenital facial palsy and external rectus palsy, several excellent reviews of the Möbius' syndrome have been published, in which various theories regarding the aetiology of the condition have been discussed.

Möbius (1892) believed that the mixture of cranial nerve lesions was due to a toxic or degenerative process. Heubner (1900) described the pathological findings in one case, in which the ganglion cells were absent from the motor nuclei of certain cranial nerves, with poor development of the formatio reticularis, olives and pyramidal tracts. Rainy and Fowler (1903) considered the primary pathology to be in the muscles, with secondary degenerative changes in the nuclei.

The bizarre combinations of cranial nerve lesions, and the associated somatic anomalies have intrigued later writers. Henderson (1939) reviewed the condition, describing the typical findings. Paralysis may be complete or incomplete, unilateral or bilateral and most commonly involves the muscles of the face especially in the upper half. External rectus palsy is common, while the muscles supplied by the third, fifth and twelfth cranial nerves are occasionally affected. Club foot occurs in one third of the cases, and defect of the pectoralis major muscle with mammary hypoplasia is a common associated anomaly. Poor general muscle development may also occur. Deformities of one hand or arm and of the ears and nose, absence of the lacrymal caruncles and glands, micrognathos, a high arched palate, vasomotor disturbances and mental defect have all been recorded. This writer discussed the analogy of the Bonnevie-Ullrich syndrome as one mechanism to account for the widespread somatic defects, but could not associate this with agenesis of cranial nuclei. Evans (1955) pointed out that all the major defects are of structures which are differentiated at the end of the second month of intra-uterine life, and considered that the primary pathology was probably in muscle. Sproffkin and

Hillman (1956) discussed the similarity to Werdnig Hoffman and Oppenheimer's disease.

Two cases of Möbius' syndrome are presented in this paper. Biochemical investigations were carried out to see if any light could be thrown on the aetiology of the condition.

Case Reports

Case 1. R.W., a boy, was born at home to a healthy multigravida. The labour was normal and at term (he weighed 6 lb.), but as he failed to breathe normally he was transferred to the Sorrento Premature Baby Unit for resuscitation.

On admission he had infrequent gasping respirations, a poor colour, poor muscle tone and excessive pharyngeal mucus. An intracranial birth injury seemed the most likely diagnosis; his appearance was odd even at this stage with marked scaphocephaly, micrognathos, low set ears, an absent left nipple and bilateral talipes equinovarus. His expressionless face was thought to be part of the generalized hypotonia.

The baby survived, unexpectedly, and sub-dural taps and a lumbar puncture did not support the original diagnosis. He could not suck and feeding remained a formidable task throughout his life. It gradually became obvious that he had bilateral facial palsy, bilateral external rectus palsy and probably weakness of some of the external ocular muscles supplied by the third cranial nerve. The intrinsic ocular muscles and the superior oblique muscles were unaffected. The masseters, the pterygoid muscles and the palatal muscles were all weak and later developed contractures. His general muscle development was poor, and he developed a marked thoracic kyphoscoliosis. The left pectoralis major was absent. There were marked epicanthic folds and he did not secrete tears. There was a complete absence of facial expression and a severe dysarthria, so that a gurgle of laughter was indistinguishable from a cry of rage, apart from his change of colour. He did not learn to sit or stand or to speak, but this seemed to be due to muscle weakness rather than to mental defect.

He made slow progress until the age of 18 months (see Fig.), but the contracture of the masseters increased the feeding difficulties and led to frequent aspiration pneumonia. He died at the age of 22 months from a respiratory infection.

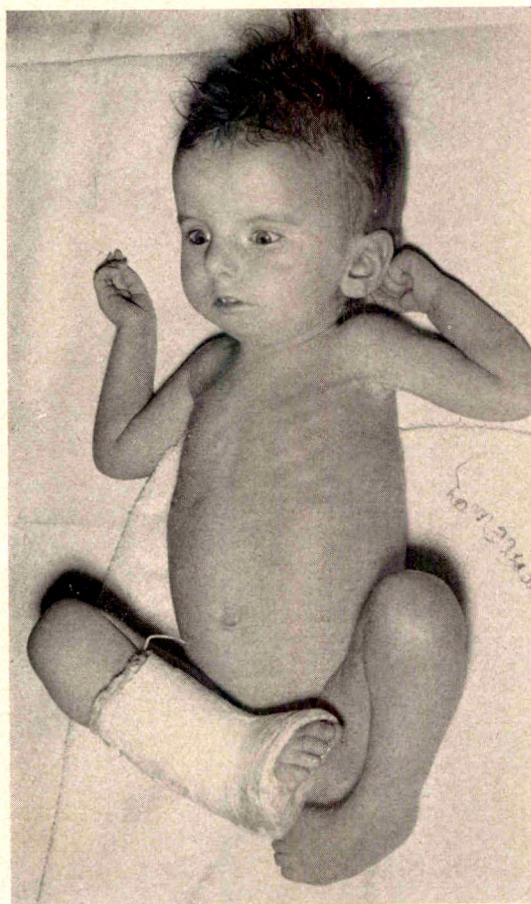


FIG.—R.W., Case 1, aged 18 months.

The serum electrolytes, calcium and phosphorus, urea and proteins were normal on several occasions. The urinary amino acid chromatogram was normal. Radiographs of the skeleton showed no defect apart from mandibular hypoplasia.

At the age of 1 year the urinary creatine was 59 mg./100 ml. (approximately 34 mg./kg./day), and the urinary creatinine 38 mg./100 ml. (approximately 22 mg./kg./day), creatine : creatinine ratio, 1.55.

A post mortem examination showed death to be due to acute bronchitis. There was generalized hypoplasia of the muscles. There was no macroscopic abnormality of the central nervous system, and preliminary examination of celloidin blocks of various areas of brain, stained by the Nissl method, showed no anatomical abnormality.

This child had a paternal uncle who died at the age of 2 years and apparently 'he looked just like R.W.'.

Case 2. S.M., a boy, was born at St. Helier Hospital to a healthy multigravida at full term and weighed 7½ lb. There was hydramnios, but the delivery was straightforward. The baby was limp and respirations

were not established until 25 minutes after birth. An intracranial birth injury was suspected and he was nursed in oxygen for the first 12 days of life. He developed sclerema neonatorum. He required tube feeding for the first six weeks of life, but then sucked well and has been breast fed since.

The lack of facial expression and generalized hypotonia, noticed at birth, persisted and, when at the age of 4 months he developed a left talipes equino-varus, the diagnosis of Möbius' syndrome seemed established. There is now bilateral facial paralysis with some sparing of the orbicularis oris. The cry is strangely monotonous but the remaining muscles supplied by the cranial nerves do not appear to be affected. The muscles of the neck, trunk and legs are poorly developed, but his arm movements are normal for his present age of 6 months. He has a high arched palate, slight micrognathos and low set ears. The equinus deformity has been kept under control with Denis Browne splints, but the forefoot varus persists and as the tendons on the anterior aspect of the left ankle cannot be felt, the tibialis anterior muscle is probably absent.

Full biochemical investigations have not been undertaken. At 5 months of age the urinary creatine was 9.1 mg./kg./day and the creatinine 6.2 mg./kg./day, creatine : creatinine ratio, 1.48.

Discussion

Creatinine is normally produced in the body from creatine by enzymic action during muscular activity. This mechanism is more efficient in adult men than in women and children, in whom a degree of creatinuria is normal. However, the excretion of creatine should not exceed 30-40% that of creatinine. In normal infants the excretion of creatine is 0.7 mg./kg./day, and of creatinine is 11-14 mg./kg./day (Nitowsky, Gordon and Tyson Tildon, 1956). Creatinuria is found in myasthenia gravis, and in the muscular dystrophies in which levels of 8-11 mg./kg./day have been recorded (Wilkins, 1957).

The high levels of creatinuria found in the two infants recorded, seem to indicate some abnormality of muscle metabolism. The very high level in Case 1 may demonstrate the severity of the affection.

The clinical similarity of the Möbius' syndrome to amyotonia congenita has been noted, and this biochemical abnormality lends support to the opinion that the syndrome is a myopathy rather than a neurological defect. The absence of the pectoralis major and the nipple on one side and the micrognathos in Case 1, the high arched palate in Case 2, and the many associated somatic defects described in the syndrome show that this is not solely an enzyme abnormality.

Although all the structures affected in this

syndrome are differentiated at the end of the second month of intra-uterine life, it is unlikely that a permanent biochemical defect could be produced by an environmental 'insult' to the foetus at this stage of development. Thus it seems unlikely that the syndrome could follow damage by migrating myelencephalic blebs as in the Bonnevie-Ullrich syndrome. Possibly an abnormality of second month 'organizers' and an enzyme defect could be produced by a single genetic mutation. The occasional finding of a familial incidence would seem to support this view of the aetiology of the syndrome.

Summary

Two cases of Möbius' syndrome are described. The finding of marked creatinuria in both infants suggests that the muscle weakness is due to a myopathy rather than to nuclear agenesis. A single genetic mutation might produce an enzyme defect and abnormal second month 'organizers'.

I wish to thank Dr. V. Mary Crosse and Dr. J. N. O'Reilly for permission to publish their cases, Dr. A. H.

Henley and the staffs of the biochemical laboratories of the Little Bromwich General Hospital and St. Helier Hospital for their help with the biochemical investigations, and Dr. J. Hoult of Dudley Road Hospital, who performed the post mortem examination in Case 1.

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PROSTATIC ABSCESS IN THE NEWBORN

BY

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During the past 14 months we have been able to confirm the occurrence of pyogenic infection of the prostate gland in three neonates admitted to one surgical unit of this hospital. As one case terminated fatally before we had appreciated the existence of such a clinical entity, it is desirable that it should be brought to the notice of others who may be confronted with a similar problem.

There is a current belief that the prostate has little clinical importance during infancy, and references are few. Bodian (1957) described two fatal cases of urinary retention due to fibroelastosis. Prostatic infection in older children has been reviewed extensively by Campbell (1937), and Winsbury-White (1949) showed such a possibility in a 9-year-old boy in whom the passage of a urethral catheter produced a purulent urethral discharge, but the diagnosis was not supported by any other confirmatory findings and there was no evidence of the periprostatic haematoma formation recently reported by Williams and Martins (1960). The following instances were in newborn babies.

Case Histories

Case 1. A male child delivered at full term, weighing 6½ lb., was admitted with retention and dribbling incontinence. Catheterization was followed by an issue of almost pure pus under pressure, and, from this, penicillin insensitive *Staph. aureus* was subsequently isolated.

Pyuria persisted for a few days but micturition soon assumed the characteristic infant pattern, the napkins being wet intermittently, and not continuously as before. Radiographic investigation after an interval revealed no evidence of obstructive uropathy.

Case 2. A male child weighing 9 lb. 11 oz. was discharged from a maternity hospital following a caesarian birth, but subsequently re-admitted as the mother had noticed increasing dysuria, continuously damp napkins, and dribbling incontinence. He was 14 days old when he was admitted to this hospital with diarrhoea, bladder distension, and complete retention of urine. There was some thick pus in the urethra, and as no urine could be withdrawn by catheter, the bladder was drained by

inserting a wide bore needle supra-pubically. Very gross pyuria was noted, and penicillin resistant *Staph. aureus* was subsequently grown from the specimen. This procedure gave considerable relief, and it seemed probable that the abscess had undergone spontaneous rupture into the bladder, but micturition did not improve, and lacked the characteristic decisiveness of infancy. Attempts to catheterize were unsuccessful as the instrument was held up in the posterior urethra, and urethrography showed a constant reduction in calibre in this area, which the radiologist reported as consistent with congenital stricture (see Figs. 1 and 2.)

This was divided by open operation, and for the past year the infant has remained well with unimpaired micturition. Pyelograms show the upper renal tracts to be within normal limits.

Case 3. A male infant, aged 3 weeks, who had been fretful from birth, was admitted to Dr. Hutchison's wards, and later transferred to the surgical side on account of increasing abdominal distension.

There was slight oedema of the lower abdominal wall, and a rather diffuse mass was palpated anteriorly on rectal examination, but the nature of this was not appreciated and a provisional diagnosis of neonatal Hirschsprung's disease was made. A distended bladder was emptied by catheter on the operating table, but unfortunately no significance was attached to this, as it is a fairly common preoperative requirement. Laparotomy revealed distension of large bowel and terminal ileum and transverse colostomy was performed. On the following day the infant died of septicaemia and an extract of the post mortem findings is as follows:

'The lower half of the small intestine and the whole of the large intestine show marked gaseous distension.

'The lungs show patchy areas of consolidation and haemorrhage.

'Both kidney pelves are moderately congested, but are not dilated, and the ureters are normal in appearance. The bladder is markedly distended. There is obvious congestion of the serosa and on opening the bladder very purulent looking urine is seen to fill the cavity. Similar purulent urine can be expressed from the urethra on compressing the bladder. At the base of the bladder a large abscess cavity measuring approximately 3 cm. by 6 cm. surrounds the urethra and spreads upwards behind the bladder and between it and the rectum (Fig. 3). The abscess appears to have arisen in the prostate.

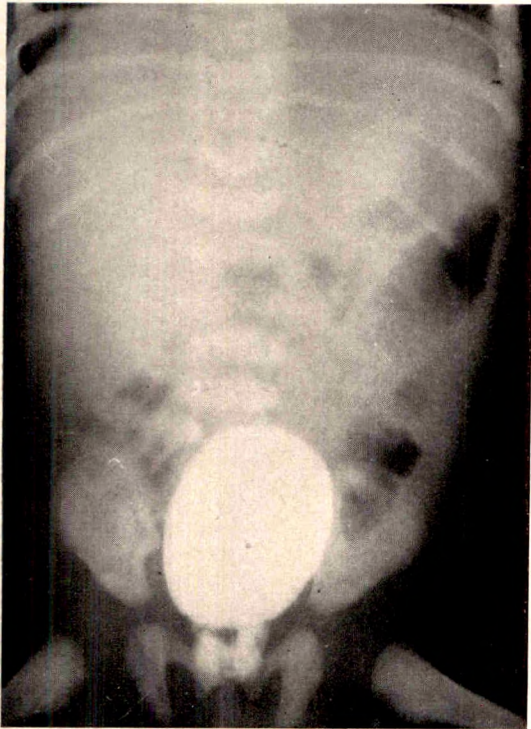


FIG. 1.

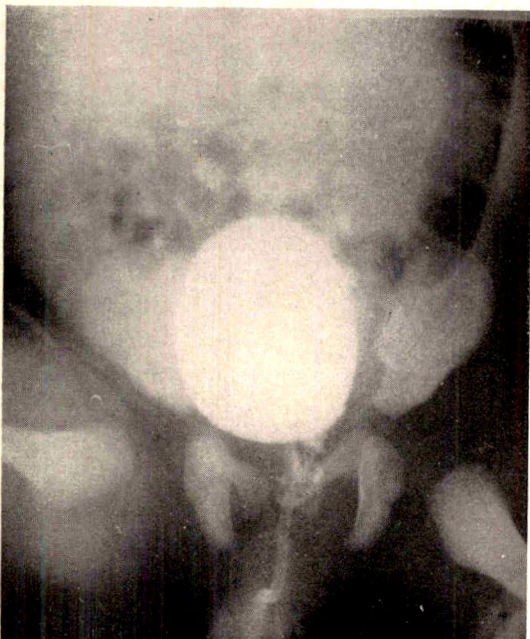


FIG. 2.

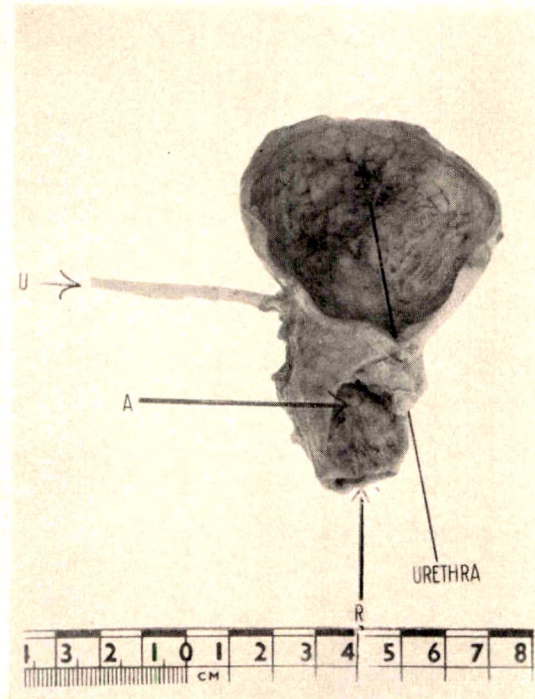


FIG. 3.

- FIG. 1.—Case 2, urethrogram of prostatic abscess.
 FIG. 2.—Case 2, urethrogram of residual prostatic abscess.
 FIG. 3.—Case 3, abscess cavity (A) between urethra and rectum (R).
 FIG. 4.—Urethrogram of child's prostate to show distension by back pressure from obstruction in distal urethra.

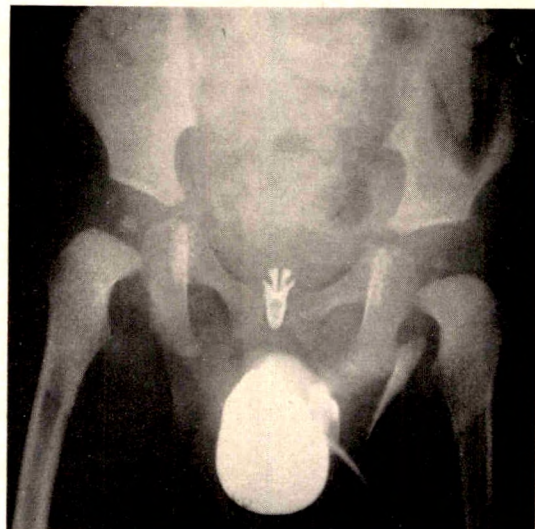


FIG. 4.

'In the colon, ganglion cells are present in normal numbers.'

HISTOLOGY. The abscess is chronic in type and beyond the pyogenic membrane there is a narrow rim of prostatic tissue, with pus cells in some of the adjacent glands. There is some diffuse infiltration of the bladder wall with inflammatory cells. The kidneys show early pyelonephritis.

BACTERIOLOGY. A swab from the prostatic abscess and a piece of lung grew penicillin resistant *Staph. aureus* and lactose fermenting coliforms in each instance, the former being sensitive to chloromycetin and furadantin and resistant to achromycin.

Discussion

Three factors may be considered to have some bearing on the development of acute neonatal prostatitis. Firstly there is the infection, to which all the newborn are at risk. It is stated by White and Dennison (1958) that in neonatal osteitis the staphylococcus has been found resistant to penicillin in over 80% of cases admitted to the Royal Hospital for Sick Children, Glasgow, and Dennison (1959) has observed the incidence of penicillin resistance to be highest in hospital-born babies. The three cases described here were all born in maternity units and penicillin resistant staphylococcus was responsible in each.

The remaining factors may be considered to play a role in determining the location of the abscess. At birth there is the squamous metaplasia of the epithelium of the utricle, prostatic urethra and prostatic glands which undergoes regression during the first week of life (Smith, 1945). The third factor, that of obstruction to the urinary outflow, was well shown in Case 2. Potter (1952) has emphasized that congenital malformation with stasis predisposes to acute infection of the urinary system, and the effect of blockage distal to the prostate is demonstrated in the accompanying photograph (Fig. 4) where we have been able to show a dilated but otherwise normal infant prostate resulting from back pressure.

Diagnosis. There should be little difficulty in diagnosis once the condition becomes established as a clinical entity. After catheterization of a distended bladder in any male infant, one should not omit rectal examination. A cystic swelling

may be felt below and in continuity with the bladder. Where rupture of the abscess occurs spontaneously, or after the use of a catheter, nothing further may be required, but urethrography should be performed, and this will show the residual abscess and indicate the site of stricture, if present. Pyogenic infection of the infant prostate may not be the rarity the literature would suggest, for spontaneous rupture into the bladder, followed by temporary pyuria, and in many cases by complete remission, is a possibility that could be overlooked. Peri-urethral abscess, secondary to infection of urethral glands has been observed in infants by White (1959) and may have originated in this manner.

Treatment. This is essentially surgical. The perineal approach to the tough distended capsule of the prostate requires special experience of paediatric urology and drainage of the infected bladder by perineal urethrostomy may be advisable, and should be continued, where necessary, until co-existing urethral stricture has been dealt with.

Summary

Three cases of acute staphylococcal prostatitis causing urinary obstruction in neonates are described. Clinical, radiograph and post mortem findings are described.

Possible causative factors are discussed and treatment indicated.

My thanks are due to Mr. Wallace Dennison who has helped me, throughout, with all cases, to Dr. Philip Rawson for radiographs and to Dr. Alistair M. MacDonald for photographs and post mortem report.

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ILIAC VEIN OBSTRUCTION DUE TO A RETROPERITONEAL ABSCESS

BY

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The occurrence of iliac vein obstruction due to a retroperitoneal abscess in infants is a rare phenomenon. This presentation of a case may be of value in the diagnosis of other cases.

Case Report

L.M., a newborn white female infant, was admitted on February 8, 1959, to Cleveland Metropolitan General Hospital as a premature home delivery. Her birth weight was 1,840 g. (4 lb.), and expected date of delivery was March 18, 1959. The mother did not have antenatal care. On the second day in hospital the baby was noted to be jaundiced. The mother's blood was group A Rh positive and the baby was group O Rh positive. On the fourth day in hospital the maximum bilirubin level was 19 mg.%. The baby did not feed well. There was no evidence of septicæmia as indicated by a negative urinalysis and normal spinal fluid. On the tenth day a femoral venipuncture was done for blood cultures and serum chemistries. The side from which the blood was drawn was not recorded. The blood cultures were negative and all the serum chemistry was within the normal range.

At the age of 25 days, swelling of the right thigh and foot was noted. The leg was oedematous and showed some discolouration. Some areas over the thigh were fluctuant but no localizing abscess was present. Inguinal nodes were not palpable. The measurements above the knees were: right 14 cm., left 12 cm. The W.B.C. was 26,850/c.mm. (neutrophils 70%). An infection was suspected. Radiograph of the hips revealed no evidence of osteomyelitis of the hip or any intra-articular fluid. The fluctuant area was aspirated but no free fluid was obtained. Material from the needle was cultured and blood cultures were also drawn. The blood cultures were negative but the aspirate grew haemolytic *Staphylococcus aureus* coagulase positive; resistant to penicillin; sensitive to erythromycin, streptomycin, kanamycin, furadantin, neomycin, chloramphenicol. Nose culture grew *Staphylococcus albus*. Chloramphenicol treatment was started.

On the 26th day in hospital circumferences of the thighs were: right 14.5 cm.; left 12 cm.; W.B.C. 18,500 c.mm. (neutrophils 54%). The right leg seemed to become more oedematous and on the 30th day measured 15 cm.;

left 12 cm.; W.B.C. 25,500 c.mm. (neutrophils 83%). The diagnosis of thrombophlebitis was entertained at this point. The infant was continued on chloramphenicol and clinically there was no change in the condition of the leg. She held the right leg abducted and externally rotated and resented having the leg moved. No abdominal masses were palpable. Rectal examination was normal. A low grade fever with temperatures of 37° C. to 38° C. now appeared.

On the 32nd day an intravenous pyelogram was done, but no pathological process was noticed. A cystogram on the 33rd day showed no evidence of displacement or filling defect of the bladder. Phlebograms were not done. A mass was now palpable in the right lower quadrant deep in the pelvis extending to Poupart's ligament. Rectal examination revealed a boggy mass in the area of the right iliopsoas muscle. The diagnosis of retroperitoneal abscess with iliac vein obstruction which had been previously entertained was now confirmed.

On the 34th day a retroperitoneal dissection was done with counterincision of the right thigh and 20 ml. of greenish yellow pus was removed. Gram stain revealed gram positive cocci and culture grew haemolytic *Staphylococcus aureus* coagulase positive; resistant to penicillin, streptomycin, erythromycin, chloramphenicol; sensitive to neomycin, kanamycin, furadantin. Pus was obtained in the operative field by pressure on the thigh and a guide introduced behind the psoas fascia anteriorly extended to the upper and medial aspect of the right thigh. 60 ml. of blood was given to the infant. On the second post-operative day measurements of the thighs were: right 12.75 cm., left 11 cm.

The chloramphenicol was discontinued on the 46th day. The infant now weighed 2,660 g. (5 lb. 14 oz.). She was discharged at the age of 2 months, completely well and when seen at the out-patient clinic two weeks later the leg was normal in size compared to the left and the wound had healed. At the age of 6 months the leg and hip were normal. Radiograph of the hip showed no dislocation or destruction of the head of the femur.

Discussion

The diagnosis of iliac vein obstruction due to a retroperitoneal abscess should be considered when an infant presents with an oedematous leg and dis-

tended veins. In 1957 Grunwaldt and Tomsovic reported two cases in male infants secondary to circumcision, and since then no further reports have appeared in the literature. In the differential diagnosis, thrombophlebitis, hip disease or, if it follows a femoral vein puncture, an infected haematoma must also be considered. The diagnosis of a retroperitoneal abscess can be made by the palpation of a mass in the lower abdomen and on rectal examination. Special investigations such as intravenous pyelography, cystograms and phlebograms may be confirmatory.

Once the diagnosis has been made surgical drainage is the only method of treatment. The aetiological organism can then be determined and appropriate antibiotic therapy instituted. It was distressing to note that the organisms isolated from this case were *Staphylococcus aureus* coagulase positive, and that they were resistant to erythromycin and chloramphenicol, the drugs most frequently used for staphylococcal infections.

The pathogenesis of this infection presents many problems for consideration. In this report we must consider the site of femoral vein puncture as the route of introduction of the infection.

Grunwaldt and Tomsovic (1957) report two cases of iliac vein obstruction in male infants both aged 3 weeks. They conclude that the primary site of infection was the circumcision site. Inguinal nodes were palpable in their cases. This suggests that the retroperitoneal infection in those cases was possibly related to skin infection, most likely the penis.

Gross (1953) reports that in some cases of iliac adenitis the portal of entry of the infection may be found on the leg or around the arms, but the initial lesion is often healed by the time the patient presents with abdominal complaints or limp. In most cases the infection skips the femoral and inguinal glands and lodges solely in the iliac group. The age range of the 20 cases reported varies from 1 to 11 years. Sex incidence is not discussed.

Reference is made in the literature to obstructive anomalies of the iliac veins with growth shortening of the ipsilateral leg (Peck, 1957). The obstruction can be either an acquired or developmental disease represented by adhesions in the retroaortic portion of the vein, or pathology due to congenital valves or septa.

Ross (1954) mentions a case of osteomyelitis of the hip with complete destruction of the head and neck of femur following a femoral venipuncture in a premature infant, but concludes that the infection of the hip resulted from a haematogenous spread from a distant focus rather than from a venipuncture in the region of the hip.

Howard (1957) reports five cases of sepsis in normal and premature infants with localization in the hip joint, but does not relate this to femoral venipuncture. He concludes that in one case the probable portal of entry of the infection was from an injection of vitamin K. Three of his five cases had received vitamin K and other subcutaneous injections.

Neuhof and Arnheim (1944) quote two cases of infected haematomas as a source of infection with formation of iliac retroperitoneal abscess.

Bosch, Kengeter and Beling (1950) discuss femoral venipuncture in 100 adult patients. They list the possible complications, namely, injury to femoral vein, penetration of a viscus in the presence of unrecognized femoral hernia, haematoma, abscess or cellulitis, penetration of psoas abscess, local ecchymosis, thrombophlebitis, phlebothrombosis or arteriovenous fistula.

Sieber and Ferguson (1959) review some of the surgical and orthopaedic aspects of infections in newly-born and young infants. From 1940 to 1957 31 cases, who had had bacterial infections of bones and joints, were found. Nine of these 31 infants had septic hips. They mention femoral vein puncture as an aetiological factor in the localization of infection in the hip joint of four infants.

This report differs from any of the previous cases described in that this occurred in a female infant, no intramuscular or subcutaneous injections were given, and the only probable portal of entry of the infection was the femoral venipuncture.

The jaundice was considered as physiological in a premature infant. In this case there was no evidence of any septicaemia as indicated by the negative blood cultures on the 10th and 25th hospital days. A haematoma at the site of venipuncture or a thrombophlebitis may possibly have been a predisposing factor in the development of this infection. It is virtually impossible to prove that the femoral venipuncture resulted in this retroperitoneal abscess, but it would seem that this is the most likely portal of entry of the infection.

When one asks other paediatricians if they have ever encountered any complication of femoral venipuncture, they may recall some cases of hip infection or osteomyelitis of the femur, but they cannot prove that this was a complication of femoral venipuncture.

In this hospital femoral vein punctures are regarded as hazardous procedures. In the first few days of life the umbilical vein can easily be entered and many paediatricians feel that adequate blood samples can be obtained by this route. It has been disturbing to note the number of positive blood

cultures obtained before starting exchange transfusions, and an investigation was conducted to determine the feasibility of using this procedure for routine blood cultures in newborns. In a report (Lipsitz and Cornet, unpublished) it will be shown how 15 out of 33 blood cultures obtained from healthy newborns were contaminated with the same organisms as cultured from the umbilical stump. It is strongly recommended that this procedure should not be used.

Summary

This report is of a case of retroperitoneal abscess with iliac vein obstruction in a premature white female infant aged 25 days. The diagnosis was made on palpation of a mass in the right lower quadrant and rectal examination revealing some boggy mass on the right side. It is most likely that the portal of entry was from the site of a femoral vein puncture.

The possible hazards of femoral venipuncture are discussed. Reference is also made to the validity of blood cultures obtained via the umbilical vein.

A review of some of the cases of hip joint pathology in premature infants does not relate the infection to venipuncture, but more likely to subcutaneous and intramuscular injections.

For permission to report this case it is a pleasure to record my thanks to Dr. F. C. Robbins, Director of Pediatrics, and Dr. F. A. Simeone, Director of Surgery. I wish to thank Dr. E. A. Mortimer, Jr., for his helpful criticism and advice.

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THE DIAGNOSIS AND TREATMENT OF HERMAPHRODITISM*

BY

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Until recently the determination of the sex of an individual was mainly based upon the gonadal structure, and the sexual individuality identified with this finding. Accordingly a person having testes was a man and one having ovaries a woman. In the hermaphrodites certain anomalies inside the genital tract were considered more or less as anatomical variations from the normal without more profound changes in the sexual structure of the organism.

Clinical investigations into the various problems of hermaphroditism have, however, changed this picture completely and have shown how much more complicated these things are and how many different factors are working together to build up the harmonious sexual individuality of a human being. Today, in cases where the sex of the child is dubious, thorough investigations must be performed before any determinations as to the sex are made or any treatment can be instituted. The investigations should determine five different aspects of the organisms: (1) the genetic sex, (2) the gonadal sex, (3) the somatic sex—including the external and internal genitalia and the secondary sexual character, (4) the hormonal status, and (5) the psychic structure, including the rearing and gender role of the patient. Only then can a satisfactory decision be made.

The present paper is intended as a short introduction to some of the clinical aspects of hermaphroditism based on a personally known group of human hermaphrodites.

Investigation

In the years 1948-1959, 31 cases of hermaphrodites were investigated at the University Clinic of Paediatrics in Copenhagen. Fourteen of these were found to be *female* and 17 *male* pseudohermaphrodites. There were no true hermaphrodites, i.e. patients with both ovarian and testicular tissue inside the same organism.

Female Pseudohermaphrodites.

TABLE 1
FEMALE PSEUDOHERMAPHRODITES

Adrenogenital syndrome	..	..	..	..	13
Origin unknown	..	..	..	..	1

All but one of the patients in the group of female hermaphrodites suffered from the adrenogenital syndrome. Nuclear sexing (Barr, 1955) showed female chromatin pattern. The clinical examination displayed more or less virilized external genitalia with a large phallus and some fusion of the labio-scrotal folds (Fig. 1). A vagina and a uterus could be demonstrated either by inspection, endoscopy or radiography (Fig. 2). In three doubtful cases laparotomy was performed. The anatomy of the internal genital tract turned out to be of three different types. In the most common type—11 cases—the vagina and the uterus opened into the posterior urethra. In one case the vagina had a normal opening into the perineum and in another it was completely closed off from the urinary tract.

High 17-ketosteroid excretion in the urine gave the exact diagnosis with minimum 5 mg./24 hours in the newborn and maximum 12 mg./24 hours when the children reached the age of 1 year or more.

A high familial incidence in the group of adrenogenital syndrome was found in our investigation with three pairs of siblings, one pair being twin girls, the other two a boy and a girl. The two boys were also suffering from the adrenogenital syndrome but, not being pseudohermaphrodites, they are excluded from this group of *female* pseudohermaphrodites.

The last patient in the group did not suffer from the adrenogenital syndrome, the 17-ketosteroid excretion being 0.5 mg./24 hours. Nuclear sexing showed chromatin positive pattern indicating that genetically the child was female. The external genitalia were rather virilized (Fig. 3). Endoscopy

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

showed a vagina and a uterus. Gonads were not palpable. Laparotomy was unfortunately not performed, but would have been necessary in order to eliminate the possibility of true hermaphroditism. The history of the mother's pregnancy revealed no androgen treatment of any sort, as is sometimes the case in these patients (Wilkins, 1957). No reason for the virilism of this child could be demonstrated.

Male Pseudohermaphrodites.

TABLE 2
MALE PSEUDOHERMAPHRODITES

Female appearance	..	..	..	..	..	7
Male appearance	..	..	..	..	..	10

In the first group of male pseudohermaphrodites all seven patients were members of two families with 'testicular feminizing syndrome', with three in one family and four in the other. In six of the cases nuclear sexing was performed showing chromatin negative pattern. Gonadal biopsy showed testicular tissue as it is seen in cryptorchism. The external appearance, especially the external genitalia, were completely feminine (Figs. 4 and 5). A small vagina and no uterus was all that was found of internal genitalia.

The oldest of these patients, a 17-year-old 'girl', showed typical feminine development at puberty (Fig. 6) with normal breast development but with amenorrhoea as must be the case in a person lacking a uterus, and with the characteristic phenomenon seen in these patients, namely, lack of pubic hair.

The 10 patients belonging to the group *male* pseudohermaphrodites of *male* appearance were found to be a very heterogeneous group, being genetically males with chromatin negative pattern, having testes proved by biopsy but with ambiguous external genitalia and persistent Müllerian ducts of various sorts. Figs. 7 and 8 show such a patient, a boy with vulvular hypospadias and with both vagina and uterus.

In four cases a sudden strong virilism at puberty was the first sign which aroused the doubt about whether a correct decision of sex had been made at birth. The genitalia until then were of such a feminine character that neither midwife, family physician nor parents had had any suspicion of dealing with a hermaphrodite. Figs. 9-13 show one of these children, who had been followed up in our department from the age of 3 until the age of 14 years. The final examination was delayed because of disease in the family. Investigation at puberty (Figs. 12 and 13) proved the patient gene-

tically to be a boy. The gonads were testes with no ovarian tissue and the hormonal status displayed an explosive hyperactive puberty with very high estrogens ($>200 <400$ Mouse/U./24 hours) and androgens (42%).

Finally the psychological investigation revealed both male and female elements in spite of the patient having been reared as a girl since birth.

Figs. 14-16 demonstrate the three other patients with female legal sex from birth, but with strong virilism near puberty. These difficult cases raise the important question of adequate approach to treatment, i.e. whether to change the sex, or remove the gonads. The problem will be discussed later in this paper.

Discussion

It is now possible, as a result of these detailed examinations of patients with ambiguous genitalia, to classify most hermaphrodites and to assemble them in different clinical groups.

The study of the chromatin pattern is an easy procedure: a buccal smear is enough for examination and, together with an analysis of the hormones in the urine, should always be undertaken, when doubt arises about the sex. Chromosomal counting, on the other hand, is still a rather complicated technique which only a few can master at present but in those cases where it can be done, the results are of great scientific and clinical value.

Gonadal biopsy as well as explorative laparotomy should be performed in almost all cases of pseudohermaphroditism except those with the adrenogenital syndrome, when other examinations have failed to give a clear answer. With the present state of paediatric surgery these procedures can safely be done in infancy. The increasing number of true hermaphrodites described in the literature demonstrates the importance of these explorations, especially with regard to gonadal biopsy, which should include incision throughout the whole length of each gonad found in the individual (Innes Williams, 1958).

The high familial incidence found in male and female hermaphrodites is well known (Morris, 1953; Holmer, quoted by Everse, 1958) and is illustrated in this material. In one of our two families with the testicular feminizing syndrome, where the parents were first cousins, no less than four out of eight children suffered from this syndrome (Fig. 17). The other four children were normal. In a branch of the same family another type of male pseudohermaphroditism was found (see Fig. 16).

Clinically two problems are met with in these patients: (1) Determination of sex at birth; (2) Decision regarding later medical and surgical treatment

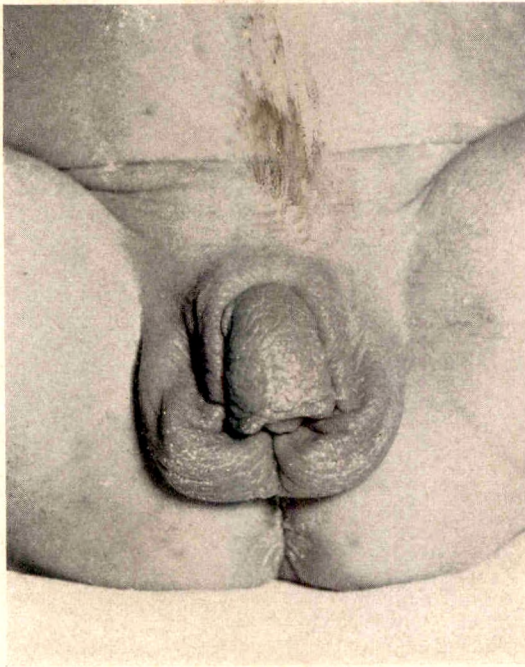


FIG. 1.

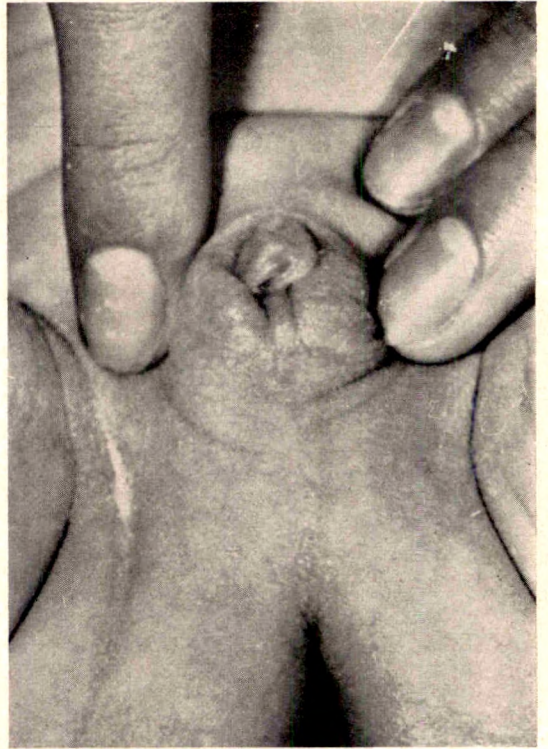


FIG. 3.

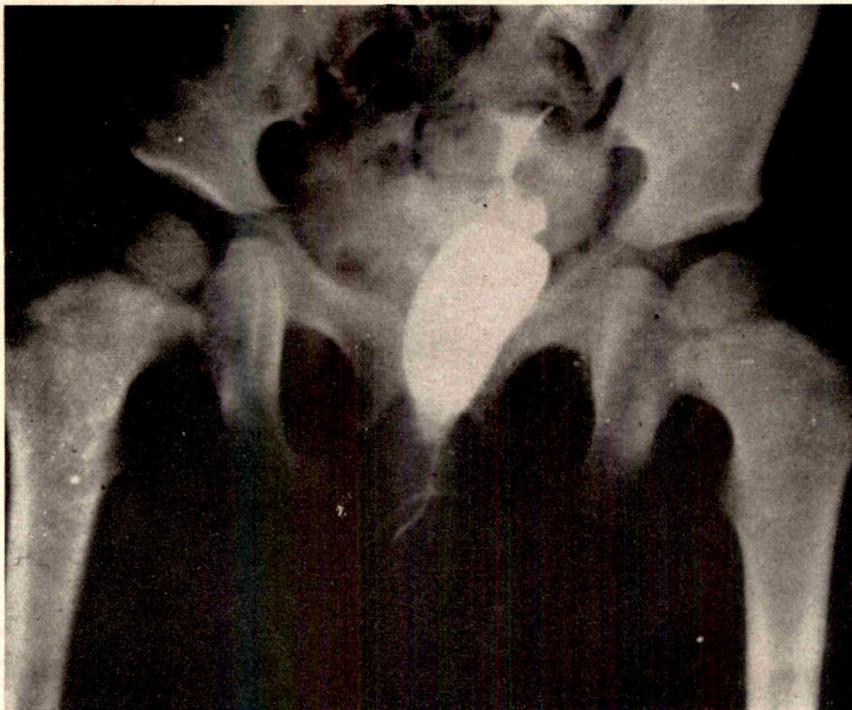


FIG. 2.

FIG. 1.—Adrenogenital syndrome.

FIG. 2.—Same patient, hysterosalpingography.

FIG. 3.—Girl with normal 17-ketosteroid excretion and virilized genitalia.

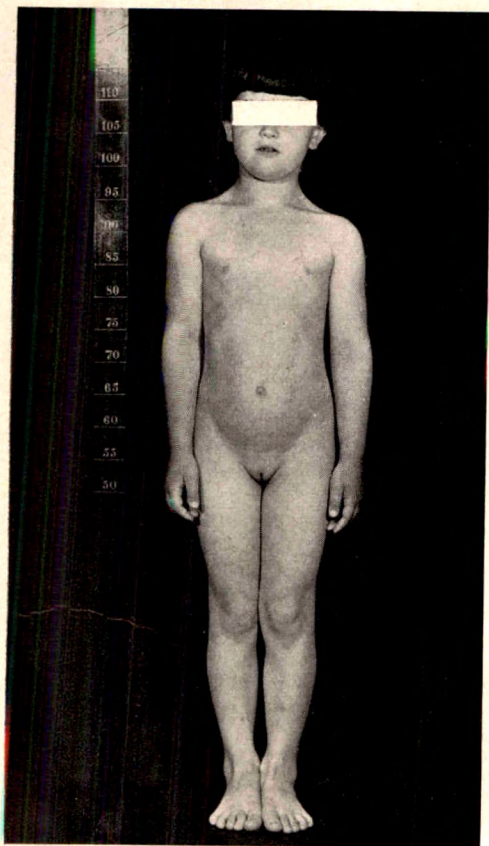


FIG. 4.

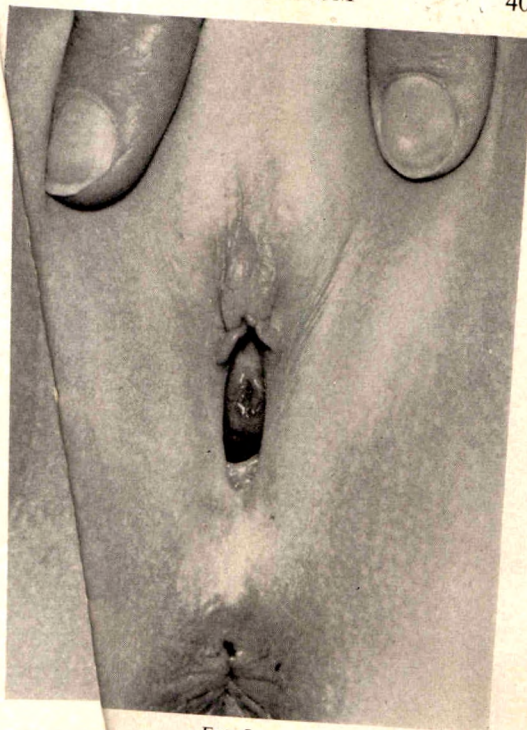


FIG. 5.

FIGS. 4 and 5.—Testicular feminizing syndrome. Appearance, including genitalia, completely feminine.

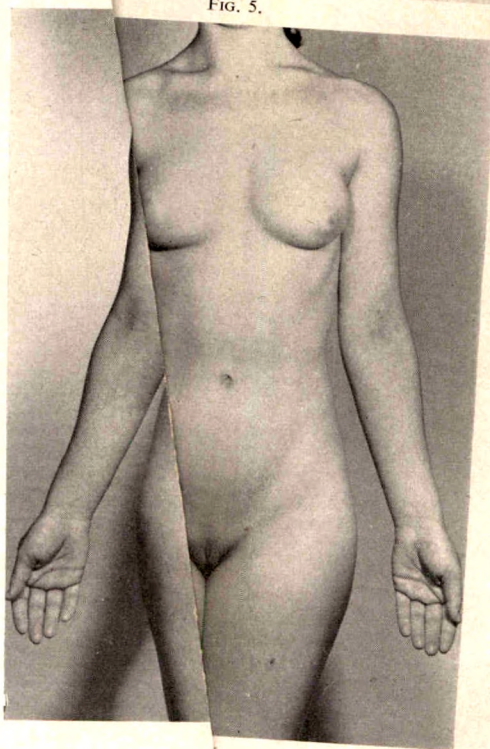
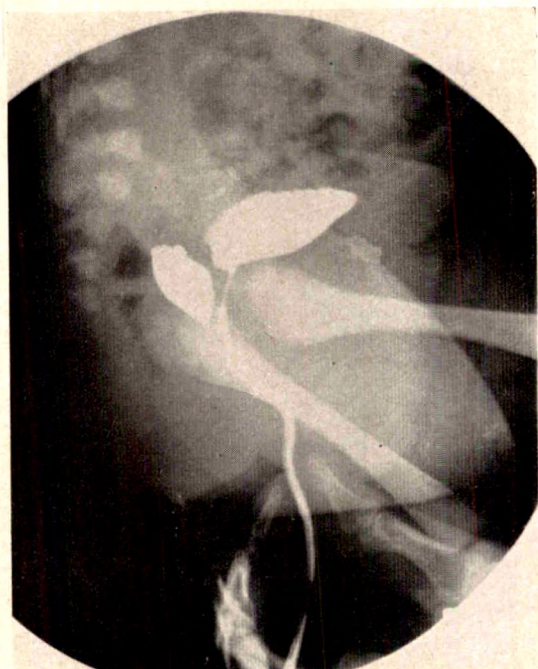
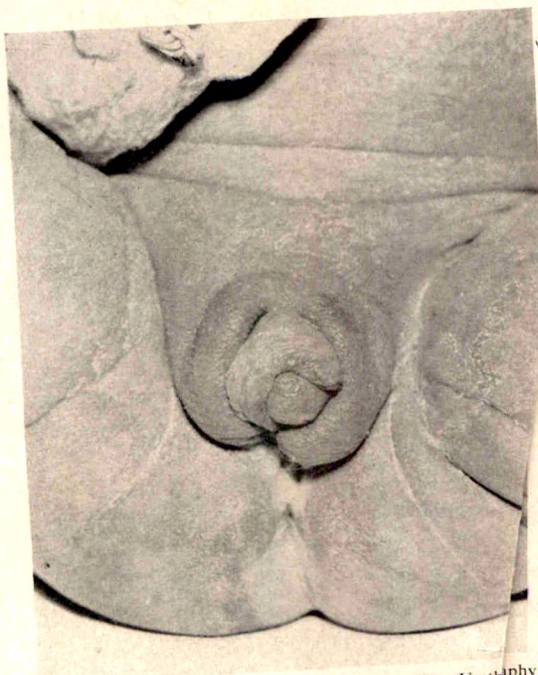


FIG. 6.—17-year-old patient suffering from the testicular feminizing syndrome. Feminine breast development but no pubic hair.



FIGS. 7 and 8.—Boy with vulvar hypospadias. Urethral surgery reveals both vagina and uterus.

FIG. 8

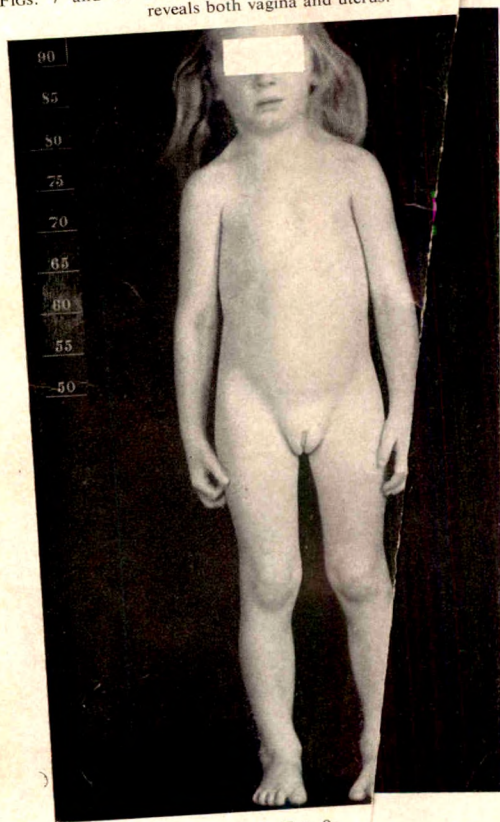


FIG. 10

FIGS. 9 and 10.—Male pseudohermaphrodite of feminine appearance.

FIG. 9.

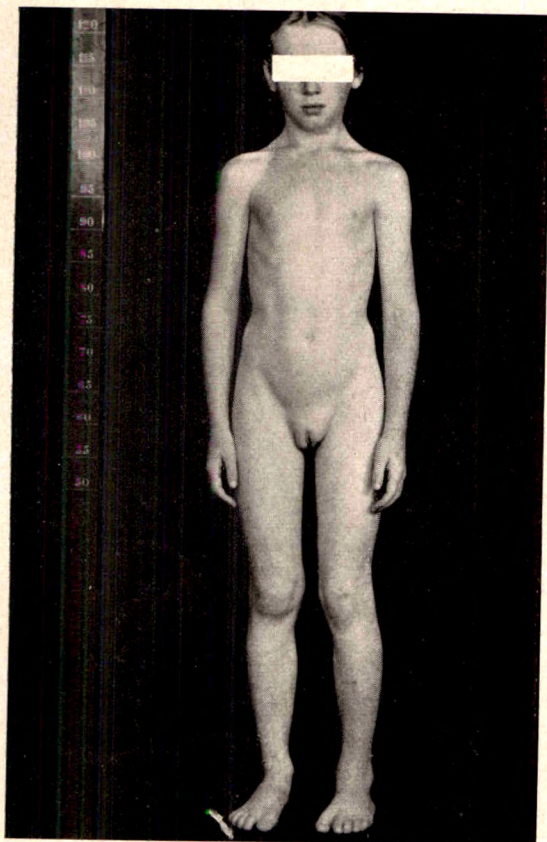


FIG. 11.

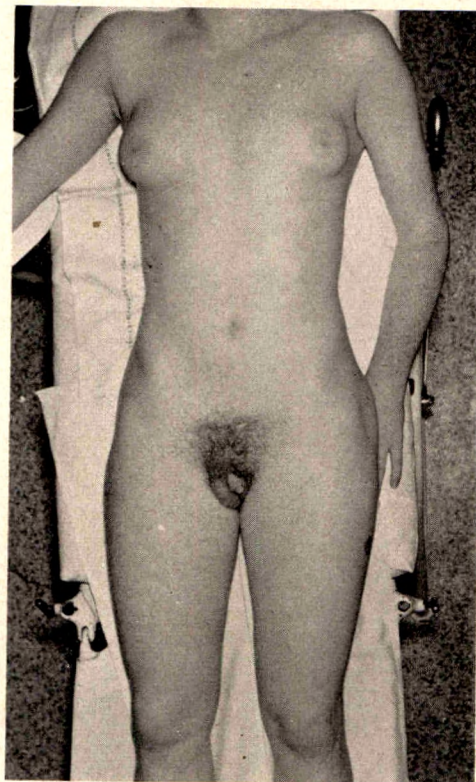


FIG. 12

FIGS. 11, 12 and 13.—Male pseudohermaphrodite of feminine appearance until puberty where strong virilism sets in (same patient as in Figs. 9 and 10.)



FIG. 13.

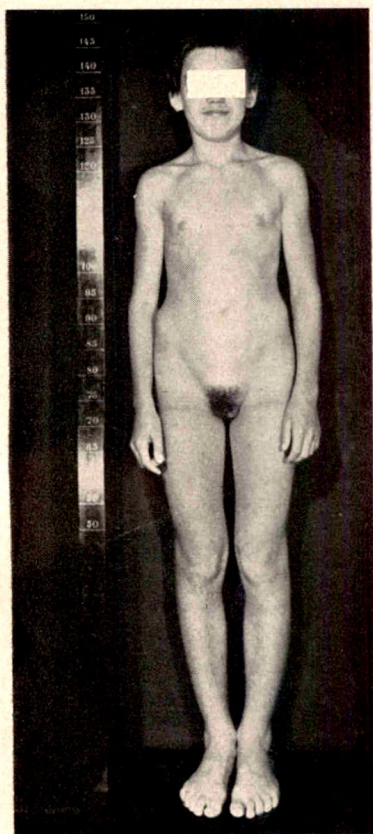


FIG. 14

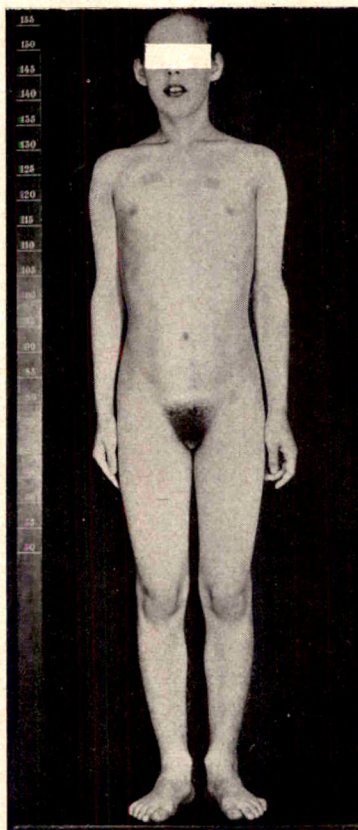


FIG. 15

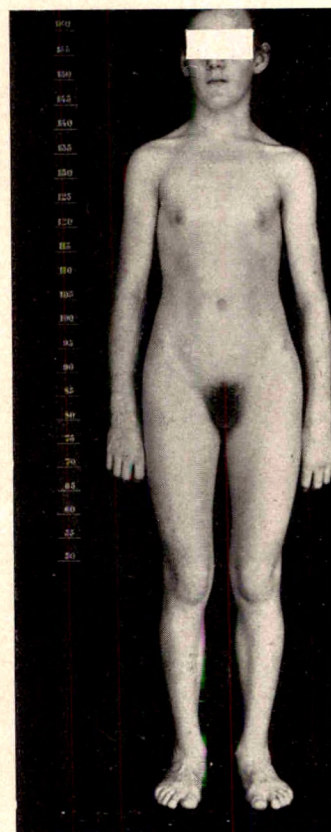
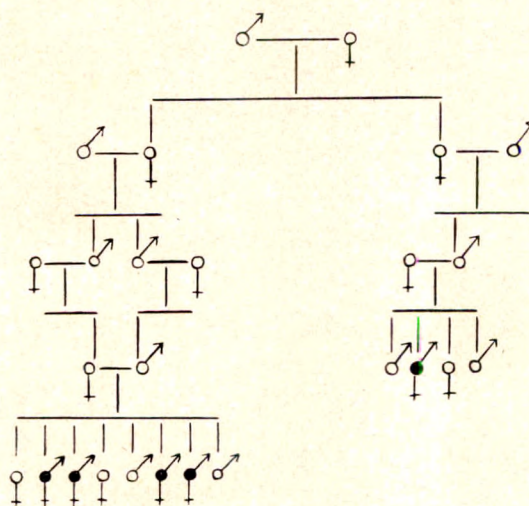


FIG. 16



Figs. 14, 15 and 16.—All patients with female legal sex at birth but with strong virilism at puberty.

FIG. 17.—Familial incidence of pseudohermaphroditism.

FIG. 17.

when signs of abnormal development appear in later childhood.

Regarding sex determination, in many cases the decision regarding the sex of the patient can be based on the findings of the genetic, gonadal and somatic sex. On the other hand the general opinion seems to favour following the anatomy of the external genitalia. If these are mainly female, the child should be registered as a girl (Fig. 18) in spite of being genetically a boy and having testes. Such a patient is easier to adapt to the female role than to the male. But the decision must be made at birth or in the first months of life.



FIG. 18.—Child with mainly female external genitalia, genetically a boy with testes.

Regarding a decision on medical and surgical treatment in infancy and later childhood this will vary considerably from case to case and must depend on what kind of hermaphrodite it is and upon the age of the patient when seen.

Adrenogenital Syndrome. Seen at birth the right sex can be chosen in accordance with nuclear sexing and hormonal status. When cortisone treatment (Wilkins, 1957) is started and continued

throughout life these girls will develop into normal women, will menstruate and can give birth to children.

Sooner or later corrective surgical procedures, comprising phallectomy and closure of the abnormal opening of the vagina into the urethra with vulvoplasty, should be undertaken. Jones and Scott, (1958) recommend the age of 1 year as being the best age for these procedures.

In the present material six phallectomies were done, the age of the children varying from 1 to 5 years. In one case it was done already in early infancy on account of emigration.

The question of the necessity of phallectomy with its possible injuring sequelae has been discussed a great deal. It is, however, the majority opinion that, as long as the phallus does not diminish in size during cortisone treatment, the operation should be undertaken at least in those cases where the phallus is of considerable size. According to Money, Hampson and Hampson (1955) this procedure does not interfere with the normal mature sexual life.

Adrenogenital syndrome in older female children reared as boys but suddenly found to be girls brings up the question of changing the sex. This is a difficult problem, and the general opinion seems to be crystallizing to the view that, after the age of 1 year, change of sex in this condition as in most other types of hermaphroditism is psychologically hazardous and should not be undertaken (Money *et al.*, 1955).

In the present investigation only one patient, less than 3 years of age, was changed from a boy to a girl and cortisone treatment instituted. This happened five years ago, but overwhelming psychic conflicts are still to be found both in the child and the parents.

In our opinion, patients with the adrenogenital syndrome, being girls from a genetic and gonad standpoint, but reared as boys, should be left as males, have the hypospadias corrected and the ovaries removed. They then feel and act like men and their gender role will clearly be male when they mature.

A patient in the present material demonstrates what can happen to the clinical picture years after puberty, if the gonads have not been removed:

L.C. was reared as a girl until 1935 at the age of 9 years the sex was changed on account of virilization with simultaneous surgical correction of the hypospadias. At the age of 30 years, when the patient was living a well adjusted life as a married man, there was a sudden development of breasts, which were removed. A year later the patient menstruated heavily from the hidden

vagina and uterus. Laparotomy was performed, a fibroma in the uterus was found and hysterectomy was carried out.

Male Pseudohermaphrodites with Female Appearance. This group includes patients with the testicular feminizing syndrome.

In childhood they are occasionally discovered during herniotomies, when a gonad is found and turns out to be a testis. In each of our two families one patient was primarily discovered this way, giving rise to a thorough examination of the others.

In these very female individuals, in whom it is known that their gender role will be that of a woman in spite of having testes and genetically being males the question arises whether the gonads should be removed or not.

This may be difficult to answer. Left in the groin, as some propose (Wilkins, 1957) they grow, become large and give an unpleasant feeling. If removed, puberty does not develop. Placed within the abdomen there will be a 10% risk for malignant degeneration (Morris, 1953). Jones and Scott (1958) advise that the gonads should be left untouched until the early twenties and then removed.

In most of our cases the gonads have been left or, during herniotomy, replaced in the abdomen and in only two cases have they been removed. The rest of our patients have not yet reached the age of 20 and the decision whether to remove the gonads or not has, accordingly, not been made yet.

Male Pseudohermaphrodites with Male Appearance. In this group the real problems are met at puberty when sudden virilization appears in children reared as girls. No simple answer can be given to the question how best to handle these patients, and many individual factors will affect the final decision. In most cases it is probably advisable to remove the gonads and make corrective plastic procedures and thus let them remain female individuals. This has been the case in three of our four patients at the ages of 13-14 and 15 years.

On the other hand the possibility of changing a girl to a boy at the age of more than 1 year cannot be ruled out. In one of our cases the child, who

was reared as a girl but genetically was a boy with testes, virilized at the age of 13 and insisted upon being changed into a boy (Fig. 15). This demand was met, but unfortunately the patient left the country so that no follow-up has been possible.

Conclusion

Patients with ambiguous genitalia at birth must immediately be carefully examined before the legal sex is decided, and in most cases both gonadal biopsy and explorative laparotomy will be a necessary part of the examination with the exception of patients suffering from the adrenogenital syndrome. The choice of sex depends more than anything else on the structure of the external genitalia.

Seen later in childhood, roughly speaking after 1 year of age, all the same examinations must be performed, but from this time it is advisable to leave the patient with the legal sex given at birth. Accordingly, corrective surgical procedures should be undertaken including excision of contradictory sex structures and in some cases removal of the gonads. The change of sex in later childhood will only rarely present a satisfactory solution of the problem.

Summary

The modern concepts of hermaphroditism are discussed based upon 31 cases of pseudohermaphroditism of which 14 were female and 17 male pseudohermaphrodites. The diagnosis and treatment in each group of patients are discussed.

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BRITISH PAEDIATRIC ASSOCIATION

Proceedings of the Thirty-first Annual General Meeting

The Annual Meeting of the British Paediatric Association was held at the Royal Hotel, Scarborough, from May 4 to 7, 1960.

BUSINESS PROCEEDINGS. Dr. Reginald Lightwood took the Chair as President, and the following members were present:

A. G. V. Aldridge, E. C. Allibone, H. Angelman, I. M. Anderson, J. Apley, Cecile Asher, R. Astley, M. W. Arthurton, Margaret Baber, A. D. Barlow, R. E. Bonham Carter, J. A. Black, A. C. Blandy, M. Bodian, J. V. Braithwaite, T. A. Brand, P. T. Bray, G. Brewis, F. S. W. Brimblecombe, R. W. Brockfield, D. Browne, N. R. Butler, W. H. Cant, I. A. B. Cathie, N. S. Clark, E. C. R. Couper, J. O. Craig, J. Craig, W. S. Craig, Mildred Creak, J. Crooks, K. W. Cross, G. Davison, C. E. Dent, E. F. Dott, D. M. Douglas, A. C. Doyne-Bell, Margaret Eastwood, J. L. Emery, J. W. Farquhar, H. V. E. Finlay, O. D. Fisher, J. O. Forfar, Isabella Forshall, A. White-Franklin, D. M. T. Gairdner, W. F. Gaisford, B. Gans, J. M. Garvie, R. R. Gordon, I. H. Gossett, E. W. Hart, C. C. Harvey, J. D. Hay, W. Henderson, J. B. Heycock, D. V. Hubble, A. Holzel, R. S. Illingworth, R. J. Isaac, N. M. Jacoby, Ursula James, R. T. Jenkins, H. Jolly, H. Everley Jones, F. F. Kane, A. C. Kendall, C. W. Kesson, A. C. Kirby, B. M. Laurance, D. N. Lawson, R. C. Lightwood, J. Lorber, R. A. McCance, Anne McCandless, P. MacArthur, J. C. Macarney, A. M. MacDonald, Agnes R. MacGregor, M. MacGregor, Helen M. M. Mackay, T. Mann, W. J. Matheson, R. M. Mayon-White, R. A. Miller, R. G. Mitchell, D. Morris, F. W. Nash, A. V. Neale, G. Nelgan, C. Newman, T. C. Noble, A. P. Norman, J. N. O'Reilly, A. P. M. Page, W. W. Payne, M. G. Philpott, J. D. Pickup, L. J. Prosser, R. J. Pugh, P. F. Rickham, E. G. G. Roberts, T. S. Rodgers, K. E. Rogers, J. Rubie, J. Sakula, B. E. Schlesinger, L. G. Scott, R. A. Shanks, W. Sheldon, Victoria Smallprice, W. C. Smallwood, J. M. Smellie, J. Forest Smith, R. E. Smith, A. L. Speirs, J. M. Stansfield, T. Stapleton, R. E. Steen, D. G. H. Stone, W. P. Sweetnam, P. N. Swift, James Thomson, John Thomson, M. L. Thomson, R. McL. Todd, C. W. Vining, D. G. Vulliamy, W. Walker, D. H. Wallace, H. R. E. Wallis, C. Warren, A. G. Watkins, D. J. Waterston, S. D. V. Weller, I. G. Wickes, R. Wigglesworth, D. A. J. Williamson, B. D. R. Wilson, O. H. Wolff, T. Wright, Winifred Young, S. Yuckin, R. B. Zachary.

Professor J. Lind, Stockholm (Windermere Lecturer) and Mr. G. J. Piller were the guests of the Association.

The following were present as guests of members of the Association:

A. W. Abramson, E. Back (Jamaica), J. P. Bound, E. T. Bowen (U.S.A.), J. E. Bowman (U.S.A.), T. Bird, R. J. K. Brown, M. F. G. Buchanan, E. A. J. Byrne, I. J. Carré, R. A. Chenoweth (Australia), Vernon Collins (Australia), J. G. Dathan, D. Danks (Australia), W. Dickson, Margaret Egan, C. G. Fagg, C. V. Feldman, C. M. B. Field, H. J. W. Fisher, M. S. Fraser, J. G. H. Frew, E. Frisell (Sweden), H. McC. Giles, R. Godfrey (Australia), E. Goldblatt (South Africa), R. A. Goodell (U.S.A.), J. L. Greaves, Mary Hallowell, O. K. Harlem (Norway), L. A. Hawkins, G. Helderweirt (Belgium), G. Hesling, D. Hilson, C. Hooft (Belgium), K. S. Holt, T. T. S. Ingram, A. D. M. Jackson, R. H. Jackson, S. Keidan, K. R. Llewellyn, June Lloyd, J. Luder, S. J. R. Macoun, R. I. Mackay, Muriel McLean, B. McNicholl, M. Brenda Morris, P. D. Moss, J. S. Oldham, M. Pacht (Israel), K. R. Parker (U.S.A.), B. W. Powell, R. Prosser, J. P. Quinton, J. P. R. Rees, T. J. Rendle-Short, I. D. Riley, A. P. Roberts, T. R. Savage, T. Morton Stewart, Dorothy Taylor, D. C. Thursby-Pelham, J. J. Tillie, W. M. L. Turner, H. Vertruyen (Belgium), O. C. Ward, B. W. Webb, R. G. Welch, R. H. R. White, B. Wolman, R. J. Young.

The Annual General Meeting was held on May 5, 1960.

The Minutes of the last meeting, which had been published in the *Archives of Disease in Childhood* were received and, subject to a minor correction, approved.

ELECTION OF OFFICERS. The following were elected:

PRESIDENT: Professor A. V. Neale

PRESIDENT-ELECT: Professor A. A. Moncrieff

HONORARY TREASURER: Professor A. G. Watkins

HONORARY SECRETARY: Dr. E. W. Hart

EXECUTIVE COMMITTEE, 1960-63:

Dr. W. A. B. Campbell, Dr. W. Henderson, Dr. G. M. Komrower, Mr. R. B. Zachary.

ELECTION OF MEMBERS. The following were elected:

HONORARY MEMBER

Dr. C. T. Potter

ORDINARY MEMBERS

A. W. Abramson (Ayrshire), Enid I. M. Addenbrooke (North Gloucestershire), D. W. Beynon (Bournemouth), J. P. Bound (Blackpool), R. J. K. Brown (London), M. F. G. Buchanan (Leeds), J. H. Burkinshaw (London), E. A. J. Byrne (Lancaster), I. J. Carré (Belfast), H. M. T. Coles (London), D. G. Cottom (London), A. A. Cunningham (Kingston, Surrey), J. G. Dathan (Stoke-on-Trent), W. Dickson (Bolton), Margaret Egan (Manchester), C. G. Fagg (Luton), G. V. Feldman (Manchester), C. M. B. Field (Belfast), H. J. W. Fisher (Hereford), R. M. Forrester (Wigan), M. S. Fraser (Aberdeen), Muriel J. L. Frazer (Belfast), J. G. H. Frew (Birmingham), A. A. H. Gailey (Belfast), H. McC. Giles (Birmingham), J. L. Greaves (Tees-side), A. G. Hesling (Preston), D. Hilson (Ashton), E. Hinden (London), K. S. Holt (Sheffield), T. T. S. Ingram (Edinburgh), A. D. M. Jackson (London), R. H. Jackson (Newcastle-upon-Tyne), S. E. Keidan (Liverpool), K. R. Llewellyn (Clatterbridge), J. Luder (Watford), S. J. R. Macoun (Guildford), R. I. Mackay (Salford), B. McNicholl (Galway), Muriel M. McLean (Clwyd and Deeside), Zina E. Moncrieff (London), M. Brenda Morris (Barrow), P. D. Moss (Blackburn), F. W. Nash (Merthyr), J. S. Oldham (Birmingham), B. W. Powell (Peterborough), J. F. P. Quinton (Norwich), J. P. R. Rees (Dublin), T. J. Rendle-Short (Sheffield), I. D. Riley (Glasgow), A. P. Roberts (Dewsbury), T. R. Savage (Romford), D. C. Thursby-Pelham (Stoke-on-Trent), J. J. Tillie (Tees-side), W. M. L. Turner (Burnley), O. C. Ward (Dublin), B. W. Webb (Taunton), R. G. Welch (Hartlepool), B. Wolman (Bury), R. J. Young (Londonderry).

The Treasurer's report and statement of accounts for the year 1959-60 were received and adopted and the auditors were re-appointed for the coming year.

The report of the Executive Committee was received and is printed below.

The recommendation of the Executive Committee 'That the title of the Executive Committee should be changed to the Council of the British Paediatric Association' was approved.

The recommendation of the Executive Committee that Rule 2 should be altered to 'It shall consist of Ordinary Members, Honorary Members and Corresponding Members. Ordinary Members shall be actively engaged in the practice or teaching of paediatrics or in paediatric research. In addition individuals who have contributed to the advancement of paediatrics in the allied specialties may be nominated for Ordinary Membership, but election

of these shall be on a restricted basis and maintain a balance between the specialties', was approved.

The President reported that Messrs. Cow and Gate had donated £200 as a grant in aid to assist members in travel on the Association's business or other travel approved by the Association. The President also reported the generous offer by Messrs. H. J. Heinz Company Ltd. of £2,500 per annum for seven years in the first instance to endow Commonwealth travelling fellowships. These offers were accepted with acclaim.

Professor A. V. Neale, on behalf of the Association, thanked the President for the part which he had played in these negotiations.

**Report of the Executive Committee
1959-60**

OBITUARY. The Association has suffered the loss of one honorary member, Sir Robert Hutchison, an original member and former President, and also the loss of two corresponding members, Professor Bronson Crothers and Dr. J. L. Gamble.

EXECUTIVE COMMITTEE

The membership of the Executive Committee during the year 1959-60 has been: Dr. J. Apley, Dr. I. A. B. Cathie, Dr. P. R. Evans, Dr. J. Forest Smith, Miss I. Forshall, Dr. A. White Franklin, Dr. E. W. Hart, Professor D. V. Hubble, Dr. F. F. Kane, Dr. R. C. Lightwood, Dr. P. MacArthur, Dr. M. MacGregor, Professor A. V. Neale, Dr. L. G. Scott, Dr. Victoria Smallpeice, Dr. J. P. M. Tizard, Professor A. G. Watkins.

The following are invited to attend as observers: Sir Wilfrid Sheldon (Advisor in Child Health to the Ministry of Health); Dr. C. Asher (Ministry of Education); Dr. J. C. R. Buchanan (Colonial Office); Dr. D. Taylor (Ministry of Health).

The Committee met in November, 1959 and February, 1960 and will meet again on May 4th, 1960. In addition to receiving reports from sub-committees (see below) the following matters were among the more important to be considered:

The Executive noted with great pleasure the distinctions conferred on Sir Wilfrid Sheldon, K.C.V.O., and Dr. Dorothy Taylor, C.B.E.

1. **MEDICAL CARE OF ADOLESCENTS.** (D. V. Hubble, R. R. Gordon, R. C. Mac Keith, Victoria Smallpeice and R. E. Smith.) The report of this sub-committee was published in *The Lancet*.

2. **CHILDREN IN ADULT WARDS.** Representation was made to the Faculty of Ophthalmologists concerning the nursing of children in adult ophthalmic wards. This was considered by the Council of the Faculty and a favourable reply was received, stating

that the views of the Platt Committee had been noted and accepted.

3. **APPOINTMENT OF PHYSICIANS TO PRACTISE PAEDIATRICS.** A survey of the number of general physicians having care of children's wards was carried out. The number was not large. In one recent example when such an advertisement was published, the Association had investigated through one of the members and had been satisfied that this was the only practical solution in this case.

4. **ADMISSION OF SPECIALISTS TO MEMBERSHIP OF THE ASSOCIATION.** The Executive Committee had considered the election of specialists to ordinary membership. A proposal to alter Rule 2 of The Association is to be submitted at the Annual Meeting to try and establish the criteria on which such elections should be made.

5. **HOME CARE SCHEMES.** A request was received from the Central Consultants and Specialists Committee seeking the views of the Association on the value of Home Care Schemes for the treatment of sick children. The Association stated that it was in favour of such schemes in general. The Executive Committee felt that it was necessary to clarify their policy with regard to such schemes. A sub-committee was set up (M. MacGregor, J. Apley, F. S. W. Brimblecombe, D. Gairdner and L. G. Scott) and has submitted two interim reports to the Executive Committee and is at present reframing this report in the light of comments which have been made.

6. **CONSULTANT PAEDIATRICIAN APPOINTMENTS.**

7. **THE PROBLEMS OF THE REGIONAL PAEDIATRICIAN**

8. **THE JOINT WORKING PARTY ON THE STAFFING STRUCTURE IN THE HOSPITAL SERVICE.**

Three closely allied problems have arisen during the past year. Last year the report of the Executive Committee indicated a keen interest in the future appointments of paediatricians and the need to train individuals for these appointments. The discussion at the Annual meeting, 1959, on 'The Problems of the Regional Paediatrician' raised further points. The Joint Working Party on the Medical Staffing structure in the Hospital Service invited the Association to submit a memorandum on the paediatric services. The President set up an ad hoc Committee (R. C. Lightwood, P. R. Evans, E. W. Hart, D. V. Hubble, M. MacGregor, L. G. Scott and A. G. Watkins) which prepared a memorandum. This was submitted to the Joint Working Party which later requested oral evidence on April 6. The Association was represented by E. W. Hart, P. MacArthur, M. MacGregor and A. G. Watkins.

The Executive Committee considered these three topics at the November meeting and initiated a survey of all paediatricians to obtain information about the present structure of the paediatric services.

The questionnaire was sent to 242 individuals having paediatric sessions and was completed by 221. The replies are still under analysis and have given a picture of the paediatric staffing of the country and have emphasized the position of the paediatrician in relation to the care of the newborn infant, the local Health Authority clinics and infectious diseases units, and have given facts concerning the difficulties in obtaining junior staff, cover for paediatricians on leave and prospects for senior registrars.

A preliminary report will be given at the Annual Meeting at Scarborough.

9. **COMMONWEALTH TRAVEL FELLOWSHIPS.** As reported last year, negotiations have been undertaken to raise money to assist Commonwealth paediatricians to visit this country each year, either at a time which would permit attendance at the Annual Meeting or for periods of post-graduate study. Negotiations have reached a hopeful stage, and it is hoped that a further report will soon be available.

10. **COW AND GATE GRANT IN AID.** Messrs. Cow and Gate have generously donated the sum of £200 for one year in the first instance. This money is to be used to assist members in meeting the expenses of duties approved by the Association.

11. **VISIT TO SWEDEN 1960.** At the February meeting the Executive Committee conducted a ballot to select the names of the party to visit Sweden in September, 1960 at the invitation of the Swedish Paediatric Association.

12. **LIAISON WITH THE BRITISH MEDICAL ASSOCIATION.** In response to representation from the Association a letter was received from the Secretary of the B.M.A. stating that the Council of the B.M.A. would bear in mind the P.B.A.'s request for consultation on paediatric problems which the B.M.A. may consider in the future, but that it could not commit itself always to do so.

13. **CASUALTY SERVICES AND UNITS.** The Executive Committee wrote to the President of the Royal College of Surgeons requesting that full consideration should be given to the proper care of infants and young children when the Royal College of Surgeons met to consider the future planning of Casualty Services and Units. This problem remains under further review.

14. **ANNUAL MEETING, 1961.** The joint meeting with the Canadian Paediatric Society

is planned for the last week in June, 1961 in Cambridge.

15. INTERNATIONAL PAEDIATRIC ASSOCIATION. A request was received from the International Paediatric Association to send a representative to Zurich to discuss 'Some selective measures which will increase definitely the standard of Paediatric education'. This was declined as it was considered that the W.H.O. inquiry had not been fruitful owing to its inherent difficulty and the unsatisfactory nature of the questionnaire.

16. OTHER TOPICS. Other topics which have been discussed are: Paediatric Education in Europe; The Fountain Hospital; The International Paediatric Association; a proposed Institute of Child Care, and arrangements for the annual meeting.

STANDING COMMITTEES

CHILD PSYCHOLOGY: J. Apley, D. MacCarthy, Mildred Creak, R. M. Mayon-White, D. V. Hubble, A. A. Moncrieff, R. C. Mac Keith, C. T. Potter.

The sub-committee has reported to the Executive Committee at each meeting. The Standing Committee is discussing liaison with the Mental Deficiency Section of the Royal Medico-Psychological Society. The Standing Committee has recommended a change in its title to 'Standing Committee on Mental Health' and this has been approved.

NURSING: Mildred Creak, R. S. Illingworth, Sir Wilfrid Sheldon, D. J. Waterston, A. G. Watkins.

The Committee has had discussions with the Association of British Paediatric Nurses and has furnished an interim report. Further discussions are to be held.

TROPICAL PAEDIATRICS: R. W. B. Ellis, R. Lightwood, A. A. Moncrieff, M. MacGregor, A. G. Watkins, Cicily Williams.

No report.

JOINT COMMITTEE WITH R.C.O.G.: P. R. Evans, J. H. Hutchison, R. Lightwood, F. J. W. Miller, A. A. Moncrieff.

Has not met since formation in 1958.

JAMES SPENCE MEDAL: P. R. Evans, C. G. Parsons, R. A. McCance, F. J. W. Miller, The Secretary (ex officio).

The Committee has met and has prepared a report.

REPRESENTATIVES:

National Association for mental health: J. Apley

U.K. Committee for Poliomyelitis: E. W. Hart.

Maternity and Midwifery Committee of the Ministry of Health: J. Forest Smith.

Joint Tuberculosis Council: W. F. Gaisford.

Standing Maternity Hospital Report Committee of R.C.O.G.: A. A. Moncrieff.

Medical Advisory Committee of Nursery School Association: L. G. Scott.

Leonard Parsons Memorial Committee: S. Graham.

National Association for Maternity and Child Welfare: A. White Franklin.

Editorial Committee, *Archives of Disease in Childhood*: see list in *Archives*.

AD HOC COMMITTEES

ACCIDENTS IN CHILDHOOD. An ad hoc sub-committee (J. O. Craig, V. Smallpeice, and S. Yudkin) was set up to consider the extent to which the Association should participate in consideration of this problem. After receiving the report of the sub-committee at the February meeting, it was decided to set up a standing Sub-Committee on Accidents in Childhood to keep the problem under constant review. The Sub-Committee includes J. O. Craig, Isabella Forshall, R. C. Mac Keith, Victoria Smallpeice, R. B. Zachary and S. Yudkin.

MEDICAL SERVICES REVIEW COMMITTEE (PORRITT COMMITTEE). The Porritt Committee requested the following memoranda which were submitted:

(a) Psychiatric Services; (b) Welfare of Children in Hospital; (c) The Medical Care of the Adolescent; (d) Report on Hospital Accommodation. An invitation was received from the Sub-Committee on Maternity and Child Health Services of the Medical Services Review Committee, to nominate a paediatrician to join the Sub-Committee. Professor W. S. Craig was invited to serve as our representative.

COMPOSITION OF MILK (COOK COMMITTEE): W. A. B. Campbell, I. A. B. Cathie, E. W. Hart, J. Thompson. Oral evidence was given by I. A. B. Cathie.

ARTIFICIAL INSEMINATION: W. S. Graig, E. W. Hart, A. P. Norman, C. O. Carter (co-opted). The Home Office Departmental Committee on Artificial Insemination (Feversham Committee) asked the Association to give oral evidence. W. S. Craig and E. W. Hart represented the Association.

INFECTIOUS DISEASES HOSPITALS: R. H. Dobbs, F. F. Kane, M. MacGregor and Dorothy Taylor. A questionnaire has been circulated and is under analysis.

SURVEYS

HYPERCALCAEMIA AND RICKETS. The survey continues and has been extended in scope to include cases of rickets up to the age of 5 years.

RIBOFLAVIN DEFICIENCY: No cases were reported.

NEED FOR A PAEDIATRIC ABSTRACTING SERVICE: This survey was undertaken at the request of the Editorial Committee of the *Archives of Disease in Childhood*, and the following replies were received:

- | | | |
|---|--------|-------|
| (a) Do you use an abstracting service today? | Yes 86 | No 36 |
| (b) Do you feel the need of a paediatric abstracting service? | Yes 52 | No 70 |

NOTICES

Tenth International Congress of Paediatrics.

The Congress will be held in Lisbon from September 9-15, 1962.

The President will be Professor C. Salazar de Souza, and the address of the Secretariat of the Congress is:

Clinica Paediatrica Universitaria,
Hospital de Santa Maria,
Avenida 28 de Maio,
Lisbon 4.

Registration Active members 1000 Escudos.
fees: Associate members 600 Escudos.

Registration period, August 1, 1961 to January 31, 1962.

If any members wish to take their families by caravan or to camp, they should write to:

Clube de Campismo de Lisboa,
Rua de Misericordia, 137-20,
Lisbos,

Portugal.

where they will obtain all the necessary information.

SCIENTIFIC SESSIONS

J. O. CRAIG (Glasgow). 'Body Build in Childhood.' The measurement, tabulation and phenotyping of 3,900 Glasgow children by Parnell's method were described. 'Hermaphrodite' tables were used, so development of one sex could only be considered relative to the other. Boys are more muscular and less fat even at 5 years, the youngest group studied. Girls seem to show a boyish growth trend around 9 years. Children from good homes are more fat, more linear and less muscular than children from poor homes at all ages studied. The consistency of the findings suggests the method is valid in childhood, and can supply a somatic background to development and disease.

JAMES CROOKS (London). 'Posterior Choanal Atresia'. Bilateral posterior choanal atresia may be the cause of death in the newly born. Such a baby has so strong an

instinct to nose breathe that he fails to learn the trick of mouth breathing and may suffocate to death within a day or two of birth. In the past probably such babies frequently died without the cause being recognized. This is less likely nowadays and recently on two occasions life has been saved by surgically removing the obstructing bone and membrane as an emergency measure within a day or two of birth. This, not tracheostomy or intubation, is the correct procedure.

J. APLEY (Bristol). 'Primary myocardial disease in infancy: clinical aspects.' In 24 infants (with autopsy in 20 fatal cases) the diagnoses were as follows: Glycogen storage disease of heart, one; aberrant left coronary artery, four; myocarditis, five; Endocardial fibro-elastosis, 14.

Primary myocardial disease is not a pathological entity, but a clinical group of disorders with some features in common. These are summarized and illustrated and differential diagnosis within the group is discussed. The importance of diagnosis is stressed, because in some types of primary myocardial disease treatment may be life-saving. Some possible approaches to research on diagnostic methods and on aetiology are suggested.

T. J. RENDLE-SHORT (Sheffield). 'A development test based on the time taken to establish a conditioned reflex.' To be published in full.

IAN M. ANDERSON (London). 'Total Pulmonary Anomalous Venous Drainage.' The various types of total pulmonary anomalous venous drainage were described and 10 cases of this condition were recorded. The clinical features of the condition were discussed and also the various ancillary methods of diagnosis such as electrocardiography, radiology, angiocardiology and cardiac catheterization. The feasibility and importance of early recognition was emphasized with particular reference to the possibility of surgical correction with the aid of modern methods of open heart surgery.

R. H. R. WHITE (London). 'A comparative study of serum transaminase levels and liver biopsies.' Serum transaminase levels were estimated on capillary blood, by King's (1958) method, in 38 children from whom liver biopsies were obtained by either needle or surgical technique. The normal range is 10-110 μ . moles pyruvate/100 ml. serum/hour. Normal levels were found in polycystic disease and storage disorders, and normal or moderately elevated levels in cirrhosis. In five out of nine infants with giant-cell hepatitis SGOT levels were higher than 320 and SGPT levels higher than 500 μ . moles, while in all nine cases the GOT/GPT ratios were < 1.0 . In biliary atresia less elevated levels were found and the GOT/GPT ratios were > 1.0 in five out of seven cases. While thus affording some guidance in obstructive jaundice, transaminase levels are not always sufficiently diagnostic to replace liver biopsy.

MARY HALLOWELL (Birmingham). 'Duodeno-jejunal biopsies in steatorrhoea.' The results of 40 duodeno-jejunal biopsies in children were reported. Twenty-nine of these children suffered from coeliac disease already established by other criteria and in all except one the

characteristic coeliac appearance of the small intestine mucosa was demonstrated. Eleven other children had a normal mucosa. Six of them did not have steatorrhoea at the time of biopsy, but the remaining five children had steatorrhoea. Of these five children one was a case of bile-salt deficiency, the second had no beta-lipoprotein in her serum and in the other three no cause was found for the steatorrhoea.

R. B. ZACHARY (Sheffield). 'Surgical aspects of a Controlled Series of Untreated Cases of Hydrocephalus, and those Treated with a Spitz-Holter Valve.' This paper reviews the failures in the treated group in order to assess which failures were attributable to remediable technical errors and which were a risk inherent in the method. The chief complication was thrombosis of the jugular vein beyond the lower end of the jugular catheter. This may be due to the insertion of too short a length of tubing into the jugular vein, or to the gradual elevation of the lower tip of the catheter due to growth of the child. The change of length in the superior vena cava, the innominate vein and the jugular vein with growth during the first few years of life is important, and must be allowed for either at the original operation or by a revision before thrombosis occurs.

A. P. NORMAN (London). 'Perceptive Deafness and Hyperbilirubinaemia.' Between the dates of May, 1953 and February, 1956, at Queen Charlotte's Maternity Hospital, 63 infants were born, in whom the total bile pigments reached a level of 20 mg./100 ml. Three of these cases have died and 14 could not be traced or failed to cooperate. Three more have not yet been investigated. In five cases audiometry was not carried out but normal hearing has been confirmed by other means. In 38 cases, audiometry was carried out: of these, three showed some hearing loss not perceptive and not associated with hyperbilirubinaemia. Five children showed perceptive high tone deafness: three of these were known to have cerebral palsy resulting from kernikterus due to rhesus incompatibility. Two were not previously known to be deaf: of these one had been affected by A.O. blood group incompatibility and the other was a premature baby with no known blood incompatibility. The maximum bilirubin concentration reached in these cases ranged from 34 mg./100 ml. in one case, to 20 mg./100 ml. in the case of the premature baby who showed no evidence of immunization. The findings of perceptive hearing loss

in these cases suggests that the maximum bilirubin concentration should be kept somewhat lower than is sometimes advocated. These findings also suggest that perceptive deafness may complicate hyperbilirubinaemia without overt signs of kernikterus more often than is realized.

JUNE LLOYD (Birmingham). 'Observations on Primary Hyperlipaemia.' In a patient with primary hypercholesterolaemia treatment with a diet rich in unsaturated fat was successful in lowering serum lipids and improving the clinical condition. In contrast, two patients with idiopathic (neutral fat) hyperlipaemia showed clinical and biochemical improvement on a low-fat diet, whereas an unsaturated-fat diet was ineffective. Levels of alpha-lipoprotein were found to be low in idiopathic hyperlipaemia and the significance of this finding in relation to aetiology was discussed.

M. S. FRASER (Aberdeen). 'The Measurement of Children's Motor Ability.' Motor performance tests yielding numerical results, make possible the objective assessment of bodily abilities and should find various uses in paediatric research. This 'neurometric' approach is illustrated by methods employed in a follow-up study (*J. Obstet. Gynaec. Brit. Emp.*, 1959, **66**, 748) of 150 children who were asphyxiated at birth and of their rigorously matched controls. At 7-13 years of age, no convincing reduction of manual dexterity was observed, although speed, strength and precision were separately measured. Subclinical impairment of locomotor co-ordination was detected by Heath's rail-walking test.

WINDERMERE LECTURE. Professor J. Lind (Stockholm) delivered the Windermere Lecture entitled 'Aspects of the functional adaptation to extra-uterine life of newborn infants'.

On the evening of May 4, 1960, the Honorary Secretary reported the results of the preliminary analysis of the replies which had been given to the questionnaire on the paediatric staffing structure in the hospital service. This was followed by a brief discussion.

K. R. Llewellyn won the Ulster Cup golf competition.

BOOK REVIEWS

Growing Up in Newcastle upon Tyne: a continuing study of health and illness in young children within their families. By F. J. W. MILLER, S. D. M. COURT, W. S. WALTON and E. G. KNOX. (Pp. 369; illustrated. 25s.) Published for the Nuffield Foundation by the Oxford University Press. 1960.

The Newcastle study was initiated in 1947 by Sir James Spence and his co-workers of the Nuffield Department of Child Health at King's College and the City Health Department with the object of providing a record of the incidence and type of illness occurring in childhood evaluated against a fully studied family and environmental background. It is offered as 'a contribution towards understanding the needs of the family in sickness and in health' as a means of preventing childhood disturbances and illnesses with their associated morbidity and mortality. The study emphasizes throughout the child as an integral part of his family and environment.

The first volume, 'A Thousand Families in Newcastle upon Tyne',* deals with the first year of life of the children in the sample. The new volume is a continuation of this work and presents the progress of 847 of the children from the same thousand family sample during the first five years of life between 1947 and 1952. The book describes the varying social and economic fortunes of the family seen against a background of life in the city and gives a general picture of the patterns of illnesses and deaths during the five years. These are subsequently described in detail and related to various aspects of the child's environment which have been fully considered in terms of housing, family and medical care. The importance of this approach can be seen in the conclusion that 'in infancy, at least, social factors largely determine whether a given infection will develop as a cold, bronchitis or pneumonia'. The significance of the family in the epidemiology of childhood illness is beautifully demonstrated in the family studies of entrenched staphylococcal and streptococcal infections. The analyses of recorded facts are well laid out in the Appendices and a short glossary of medical and local terms is provided. There are some excellent photographs which add to the clear descriptive pictures.

The value of the book lies not only in its clear presentation of the natural history of childhood disease fully evaluated against its environmental and epidemiological background, but in its record of contemporary social life. The care and consideration with which the families have been treated in order to obtain these facts are evident throughout the book and are stressed by the attitude 'We hope that during these years we have been sufficiently sensitive to the privileges we have been so generously

given' and also by the degree of cooperation from the families with only seven withdrawals from the survey during the five years. The high incidence of disturbance in the human environment, with 53% of the children having at least one adverse factor in deprivation, deficiency and dependence, and 8.3% of children whose families are deeply involved in all three factors, stresses the real need for family guidance, especially in the sphere of personal relationships. Education of parents with regard to the recognition of illness and the avoidance of contact with cases requires greater attention than has been previously given in order to reduce further illness and morbidity in children. The important role of family doctor emerges in its true light and the need for improved medical education in order to enable him to fulfil this role adequately is made apparent.

It is hoped that as the study advances greater attention might be paid to the physical growth of these children; a few simple measurements accurately taken by health visitors at regular and more frequent intervals would provide a unique opportunity for longitudinal growth study in so large and representative a sample of children whose background and development is intimately known.

This book is strongly recommended to all those concerned with family health, in particular, medical students, family doctors, health visitors and sociologists and to any who seek an outstanding study to provide a model for any similar work.

Brucellosis in England. By HUGH R. E. WALLIS. (Pp. 140; 9 figs; Index. 25s.) London: A. S. O'Connor & Co. Ltd.

Dr. Harold J. Harris states in the preface to this book, 'The case histories given so vividly but with such admirable conservation of verbiage (which indeed pertains throughout the book) serve to call attention to the manifold symptomatology of brucellosis . . .'; unfortunately the greatest fault of this book is its failure to present concise and exact data and observations. Dr. Wallis quotes extensively from the classic paper of Barrett and Rickards but the evidence he presents is not as convincing as was theirs. One of the most interesting sections is the brief historical review.

There are several errors which point to poor editing, which is surprising in a monograph which is obviously a labour of love. It is irritating to find 'see Table 1 on pages 30-31' when Table 1 is on pages 88-89; or to read 'the urine may show a few to many leukocytes'; or that a very good positive skin reaction 'remained for a week and the centre became almost neurotic'. Percentages are often given to the second decimal place but as the thesis is mainly developed on the data from 35 cases, this is hardly justified; it would appear that Dr. Wallis might have been bewitched by his own figures as when he

* Published for the Nuffield Foundation and the Nuffield Provincial Hospitals Trust, 1954. 10s. 6d.

refers to the examination of 17 specimens of sera, obtained after skin tests had been performed, and he found that '14 (82.35%) showed a significant rise in titre'.

It is stated that blood culture is rarely positive, but it is surprising that there is no mention of a blood culture being performed on Case 4, which was diagnosed early in the disease when the titre of agglutinins was high; the reviewer has always found that such a case has given positive blood cultures.

However, this book emphasizes the importance of excluding a diagnosis of chronic brucellosis in patients who have 'rheumatic' symptoms and it is valuable also because it restates the value of brucellin skin tests when these are combined with serial agglutination reactions; the author also demonstrates the danger inherent in unpasteurized milk.

The Royal Edinburgh Hospital for Sick Children, 1860-1960. By DOUGLAS GUTHRIE with various contributors. (Pp. 75+xii; illustrated. 17s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1960.

The Royal Edinburgh Hospital for Sick Children celebrates its Centenary this year, a fact which will be acclaimed by many outside the intimate circle of those privileged to speak affectionately of the 'Sick Kids'.

The story of this famous hospital is an epic which compels the telling as the first hundredth milestone passes. We must all be grateful to Dr. Douglas Guthrie for his undertaking and congratulate him warmly upon his achievement. He has given us a delightful little book which is assured of world-wide interest.

The author has been assisted by seven other distinguished contributors. This could have been a problem, but any risk of scrappiness or repetition has been skilfully avoided. History unfolds smoothly, crucial episodes and vital personalities are admirably high-lighted, and the result is a most readable record of great historical value. From its birth, a hundred years ago, the Hospital has grown gloriously in the setting of the Edinburgh School of Medicine of which it must always be an essential bulwark. Today state control brings a new challenge, as Professor Ellis indicates in his wise assessment of the future. There are many in the hospital world outside Edinburgh who chafe under the torpor of bureaucracy and pray for a renaissance in high places of the courageous vision which inspired the Voluntary Hospital System. Wherever re-education may be necessary, Dr. Guthrie's book affords a timely stimulus.

Maternal Disorders related to Fetal Stress, Perinatal Death and Congenital Defects. Selected References 1952-58. (Pp. v+33.) Bethesda, Md.: U.S. Dept. of Health, Education and Welfare. Copies available from the Library, National Institutes of Health, Bethesda 14, Maryland, U.S.A.

This list of references is concerned with those maternal disorders which bear on the foetus and the perinatal period and which cause congenital defects. There are some 413 of them but as the articles included are all in the English language, the publication is of rather doubtful value.

Der Liquor Cerebrospinalis in Kindesalter. By H. SCHÖNENBERG. (Pp. viii+175; 43 figs. DM. 29. Stuttgart: G. Thieme. 1960.

This is the first comprehensive monograph on the cerebrospinal fluid written by a paediatrician for paediatricians. It is divided into two parts—the first giving the *general* data of physiology and pathology whilst the second contains a full account of the fluid findings in *each disease*. In both parts the presentation of detail and the discussion of the theoretical aspects are well balanced. The main subjects of part one include barriers, testing for permeability, technique of specimen taking, pressure, cells, proteins, electrophoresis, colloid reactions, sugar, sodium chloride, lipins, lactic acid, amino-acids, physico-chemical properties, enzymes, vitamins, immunology, the normal, subnormal and pathological liquor in general and the liquor syndromes (meningitis, encephalitis). The second part is devoted to a description of the fluid changes integrated with the pathology of all known central nervous diseases of childhood including *Listeria* infection, actinomycosis, leptospirosis, mycoses, toxoplasmosis, foreign body meningitis and viral encephalomyelitis (down to cat-scratch disease).

The author draws from personal experience, and his presentation of the possibilities and limitations of liquor diagnosis is critical. A list of references running to 13 pages concludes the book. It will be welcome to paediatricians and clinical pathologists.

X-ray Diagnosis of the Alimentary Tract in Infants and Children. By EDWARD B. SINGLETON. (Pp. 352. 83s.; 11.00\$.) London: Interscience Publishers Ltd. Chicago: Year Book Publishers Inc. 1959.

This is by far the most realistic and comprehensive book on the radiology of the gastro-intestinal tract in children that has yet been published. It is very readable and approaches the subject from the viewpoint of a logical application of radiographic techniques to the problems of children's disease. This is perhaps the chief value of the book. The clinical background, including the developmental, anatomical and physiological factors involved in each problem, is first excellently surveyed. The position of radiology in each case is then given in detail, and the radiological contribution discussed in an unusually able manner against the clinical background. At the end of each section there is a list of references, and the titles and subtitles are clear and numerous.

The illustrations are of the same high quality as the text and excel those found in most textbooks of radiology by concentrating on the problem at issue. They are unusually effective, and there are plenty of them.

This work can be recommended without reservation and will be found of the utmost value to both clinicians and radiologists. It should go far to clear up a lot of the uncertainty that still prevails as to the role radiology plays in the diagnosis of alimentary disease in the young. The author is to be congratulated.



HISTOLOGICAL CHANGES IN THE DUODENAL MUCOSA IN COELIAC DISEASE

REVERSIBILITY DURING TREATMENT WITH A WHEAT GLUTEN FREE DIET

BY

CHARLOTTE M. ANDERSON

From The Royal Children's Hospital, Melbourne

(RECEIVED FOR PUBLICATION JUNE 23, 1960)

From the examination of biopsy material Sakula and Shiner (1957), Rubin, Brandborg, Phelps and Taylor (1960a) have demonstrated histological changes in the duodenal mucosa of patients with coeliac disease or wheat gluten intolerance and shown that these changes are identical with those demonstrated by themselves and others in adult patients with idiopathic steatorrhoea. The changes recorded by all observers in both conditions are very similar but vary in severity in individual patients. However, the interpretation of the nature of these changes and whether they are primary anatomical ones or secondary to the effect of ingested food substances has not been clearly demonstrated and is still a matter for conjecture.

Shiner and Doniach (1960) in their most recent publication state that the histology suggests defective formation of villous epithelial cells and describe the picture as villous atrophy of varying grades. They suggest that the changes are primary and irreversible and the harmful effect of wheat gluten is superimposed on this primary atrophy. Rubin, Brandborg, Phelps, Taylor, Murray, Steimler, Howry and Volwiler (1960b) also suggest that the lesion is an irreversible one and that it may persist throughout life; they agree, however, that their evidence for this is incomplete, as in two patients the lesion appeared to improve with treatment.

The present study demonstrates the histological changes in the duodenal mucosa in biopsy material from a group of newly diagnosed young coeliac patients and the complete or partial disappearance of these changes during the first year of treatment in patients of this group from whom subsequent biopsies have already been obtained.

Material and Method

Clinical Material. From January, 1959 to April, 1960, a single duodenal mucosal biopsy was obtained

from each of 17 children newly diagnosed as cases of coeliac disease or wheat gluten intolerance. All children were subsequently treated by excluding wheat gluten from the diet and were followed carefully. In 11 of these patients biopsies have been repeated at certain intervals during treatment.

Criteria for initial diagnosis were rigid and only children showing the features of clinical history and physical examination recorded in previous publications (Anderson, Frazer, French, Gerrard, Sammons and Smellie, 1952b; Anderson, 1959) were included. Laboratory investigations demonstrated steatorrhoea by fat balance, normal quantities of pancreatic enzymes in duodenal fluid using the methods described previously (Anderson *et al.*, 1952b), normal sodium and chloride content of sweat determined by the method of Anderson and Freeman (1958). Gastro-intestinal infection and tuberculosis were excluded by relevant tests. All patients improved rapidly and showed normal clinical progress on a wheat gluten free diet.

During the period of treatment the diet was carefully checked at each visit. At the time of each subsequent biopsy, a three-day stool collection was examined for total fat excretion; haemoglobin, weight, height and clinical progress were recorded.

Collection of Biopsy Material. Biopsies were obtained by the multipurpose suction biopsy tube of Brandborg, Rubin and Quinton (1959) without the mercury containing balloon attached. Patients were fasted overnight and the tube passed orally while the patient was under basal anaesthesia with rectal bromethol (100 mg./kg.). The end of the tube was manoeuvred into the duodenum under fluoroscopy using an image intensifier and television screen. Radiation table dose was between 0.5 and 1 roentgen in young children and did not exceed 2 roentgens in the older children; the procedure was abandoned after these levels had been reached, if the tube was not in position. Specimens were taken from the second, third or fourth part of the duodenum and were about 3.5 mm. in diameter, consisting of mucosa and muscularis mucosae with a minimum of submucous tissue.

It has not been found easy with this type of tube, within the limits of radiation dosage and with the tube passed by mouth instead of nose, to obtain specimens beyond the duodenojejunal flexure in young children. Therefore in this paper the duodenal mucosal changes only are described.

No post-biopsy complications were encountered. The use of basal anaesthesia helped in the ease of the procedure and in abolishing any unpleasant memories of the event from the minds of the children, allowing follow-up material to be obtained more readily. A single biopsy specimen only from each child was examined as success in obtaining more than one specimen at a time was very limited.

The method for orientation of the biopsy specimens, fixing and H. and E. staining followed substantially those described by Rubin *et al.* (1960a) and, as these authors recommend, sections from the central core of the specimens were examined to avoid tangential artefacts. The sections were examined, and compared with reference to particular features by the author, who was aware of their origin and also by two pathologists of the Royal Children's Hospital, Melbourne, Dr. A. Williams and Dr. L. Taft, independently, and without knowledge of their origin. Quantitative counting of villi as described by Rubin *et al.* (1960a) was not carried out.

Duodenal biopsies from children without organic disease have been obtained under identical conditions and examined in the same way. The appearance described by Shiner and Doniach (1960) and Rubin *et al.* (1960a) for normal duodenum have been confirmed, but for the sake of brevity are not illustrated again in this paper.

Results

Initial Biopsy Specimens. The duodenal mucosa was abnormal in all patients. Low magnification microscopic examination showed a characteristically flat surface to the mucous membrane. In most

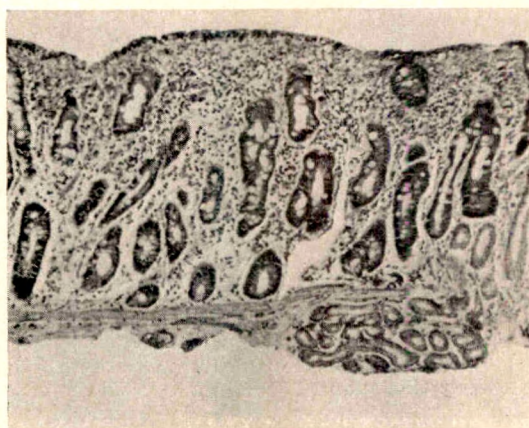


FIG. 1.—Example of duodenal biopsy ($\times 37$) from Group I. Case 5—moderately severe ($+++$) changes—long flat areas between crypts—irregularity of surface epithelium.



FIG. 2.—Example of duodenal biopsy ($\times 35$) from Group II. Case 14—straight edge to mucosal surface—short stumpy villi—minimal change in epithelial cells.

cases villi were completely absent, replaced by broad flat areas between crypts (Figs. 1, 3, 7 and 11). In a few, flattened stumpy villi were present but these did not show branching nor project above the surface (Fig. 2). The chief characteristic was the straight flat edge of the mucosal surface. In the majority, surface epithelial cells were altered, the single layer of tall columnar cells with basal nuclei being replaced by flattened cells with irregularly placed nuclei, sometimes several layers of cells giving a stratified appearance. Usually very few goblet cells were present on the surface, but in the crypts epithelial cells had a more normal appearance and goblet cells were present. The lamina propria was considered of normal thickness but in some cases a deceptive increase in thickness was suggested because the lamina was not drawn up into the villi. The lamina propria contained many plasma cells, some eosinophils and occasional polymorphonuclear cells, but there was considerable variation in the density of cell population among individual cases, this being often about the upper limits of normal, but sometimes greater than normal.

As only one biopsy specimen was obtained from each patient a strict quantitative assessment of the mucosal changes seemed unwise since it is probable that these changes vary from place to place in the gut. However, the biopsies did show individual variation and the degree of severity of the changes was rated according to a series of pluses ($+$), by the three observers, independently, with very minor disagreement. In Table 1 this rating is compared with certain clinical findings. Only the most characteristic features were considered in determining the rating; for instance, degree of

TABLE 1
CLINICAL FINDINGS IN 17 CASES OF COELIAC DISEASE COMPARED WITH SEVERITY
OF DUODENAL MUCOSAL CHANGES IN BIOPSY SPECIMENS

Case No.	Sex	Age in Years	Approximate Duration of Symptoms	Weight (kg.)	Hb g./100 ml.	Fat Excretion (g./day). Average 5 days	Severity of Histological Changes in Duodenal Mucosa
<i>Group I</i>							
1	F	1 year 6 mths	4 mths	10	10	9	++++
2	F	1 year 8 mths	8 mths	8.2	9.9	10.1	++++
3	M	10 years 1 mth	Years	32	14.1	16.3	++++
4	M	10 years	Years	24	11.5	13.5	++++
5	F	1 year 6 mths	2 mths	10	10	17	++++
6	M	4 years 5 mths	3 years	15	8.4	30.4	++++
7	M	6 years 8 mths	Years	18	9	10.4	++++
8	M	4 years 11 mths	Years	18	10.1	19	++++
9	F	9 mths	3 mths	9	12.1	9.4	++++
10	F	1 year 10 mths	2 mths	10.6	11.5	30.0	++++
11	M	1 year 2 mths	1 mth	7.5	10.1	6.4	++++
<i>Group II</i>							
12	M	6 years 4 mths	Years	14.5	13.5	14.8	++
13	M	1 year	3 mths	8.5	10	6.5	++
14	M	1 year 9 mths	Mths	9	9	11.5	++
15	F	2 years 11 mths	Mths	12.6	9	19.6	++
16	F	1 year 9 mths	2 mths	7.7	10	12.7	+
17	F	2 years	Mths	10	9.3	8.8	+

++++ Most severe—disorganization of surface epithelium with stratification, no villi.

+++ Occasional flattened villi, otherwise as above.

++ Surface epithelium less severely disorganized, no stratification. Occasional flattened villi.

+ Least severe, surface epithelium still tall columnar with some flattened areas. Villi stumpy and poorly differentiated from crypts. Straight edge to mucosa.

TABLE 2
CLINICAL FINDINGS IN 11 TREATED CASES OF COELIAC DISEASE (FROM TABLE 1)
AND DEGREE OF IMPROVEMENT IN DUODENAL BIOPSY

Case No.	Duration of Treatment	Strictness of Diet	Weight (kg.)	Hb g./100 ml.	Fat Excretion (g./day)	Biopsy—Degree of Improvement
1	0	Very occasional lapse	10	10	9	—
	9 mths		13	13	5.3	++
2	0	Occasional lapse	9.9	8.2	10.1	—
	9 mths		12.0	11.8	3.2	++
5	0	Strict	10	10	17	—
	9 mths		17	11.3	6.6	+
6	0	Very occasional lapse	15	8.4	30.4	—
	3 mths		18	9	5.6	++
	12 mths		20	11	6.5	+++
7	0	Strict	18	9	10.4	—
	3 mths		20.4	10.1	5.2	++
	11 mths		22	11.5	6.3	+++
8	0	Took other children's food occasionally	18	10.1	19	—
	11 mths		22	12.3	11.7	+++
10	0	One cake just before second biopsy	10.6	9.5	30	—
	3 mths		15	11.7	11	+++
11	0	Strict	7.5	10.1	6.4	—
	3 mths		8.5	11.3	2.4	+++
12	0	Strict	14.5	13.5	14.8	—
	3 mths		17.2	12.3	3.8	++
13	0	Strict	8.5	10.0	6.5	—
	3 mths		10.8	11.8	1.5	+
14	0	Only fair supervision	7.7	10.0	12.7	—
	11 mths		10.7	—	5.1	++

+ Villi present but still stumpy, surface epithelium tall columnar cells.

++ Villi longer but not quite normal, surface epithelium normal.

+++ Villi and surface epithelium within normal limits.

Fat Excretion. Initial: Average of five days. In-patient.

Follow-up: Average of three days. Usually out-patient.

Diet: As far as could be assessed by comprehensive questioning of mother.

disorganization of surface epithelium and state of the villi.

Table 1 shows that the cases fall into two groups, the first 11 in whom the changes were severe or

moderately severe, and the remaining six in whom the changes were definitely milder, particularly the change in surface epithelium. The majority of the older children and therefore those in whom

symptoms had been present for the longest time, are in the first group. However, this correlation is not complete as there is one older child with mild changes (Case 12) and two quite young children (Cases 1 and 2) with very severe (+++++) changes. Among the first group the degree of malabsorption in most cases appears to be rather more severe than in the second group but this correlation is still not extremely close, Cases 12 and 15 showing moderately severe malabsorption and Cases 1, 9 and 11 showing a milder degree of malabsorption. The degree of clinical illness did not correlate with the changes, as some of the very young children of the second group showed quite severe symptoms, whereas the older children in the first group showed milder clinical symptoms which no doubt accounted for their late diagnosis. The two 10-year-old boys had been diagnosed in early infancy, treated for one or two years, and had then resumed a normal diet and were considered fairly well until readmitted for investigation of recurrent abdominal pain.

Biopsy Specimens During Treatment. In Table 2 the patients from Table 1 who had biopsies repeated during treatment are listed with records of fat excretion, haemoglobin and weight gain at those stages, together with some indication of the degree of improvement in the appearance of the mucosa. In all cases alteration and improvement towards normal were noted, but to a variable degree, resumption of a normal or near normal appearance of the surface epithelial cells being the most constant and marked feature. Tall columnar cells interspersed with goblet cells are again present. Villi reappeared in each case but were very variable in their size, shape and number. Again a rating has been given to each of the subsequent biopsies, according to the degree of improvement in the surface epithelium and the villi. In five (++++) the biopsies were considered to be within normal limits; in four (++) the surface epithelium was normal in appearance but the villi were considered to be still somewhat shorter and wider than normal. In two the improvement was slight (+) villi being very short and blunted but there was definite improvement in the appearance of the surface epithelium which was of the normal tall columnar type. The degree of improvement did not correlate well with any particular clinical feature, but was present after three months' treatment (Cases 10 and 12) to a similar extent, as after nine to 12 months' treatment (Cases 6 and 7).

Dietary restriction was well carried out but in most patients occasional lapses took place, more particularly in the school age children who accepted

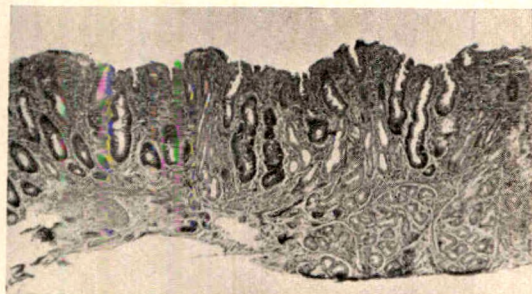
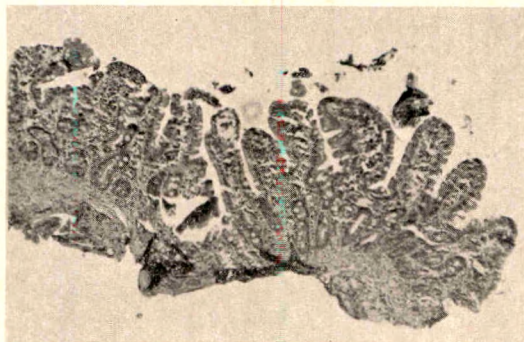
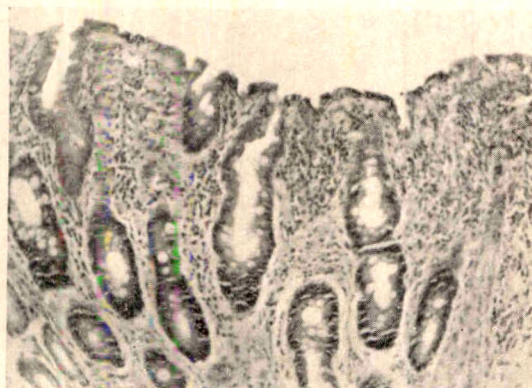
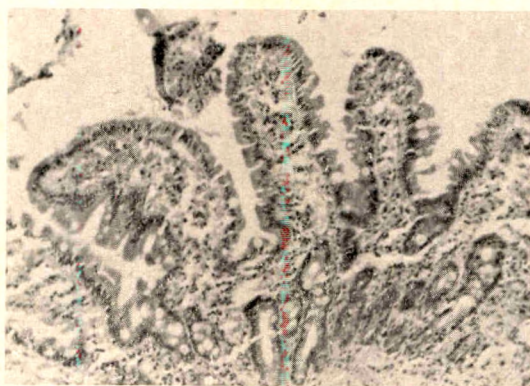
offerings from schoolmates, or because the mother was unaware that certain prepared and tinned foods contained gluten. Absorption was not always quite normal when the biopsies were repeated and these dietary lapses may have contributed to this. Marked clinical improvement had taken place in each case as can be seen from the weight and haemoglobin gains, but the biopsy did not always show a comparable degree of improvement.

Figs. 3 to 14 give visual evidence of the improvement in three patients. Low magnification pictures show the overall appearance of the biopsy with reappearance of villi during treatment, and higher magnification illustrates the detail of epithelial cells and lamina propria. Figs. 3 to 6, from Case 6, illustrate the return to a normal or near normal appearance in the specimen taken 12 months after the beginning of treatment. Figs. 7 to 10, from Case 10, illustrate biopsies taken initially and after only three months of treatment and show a return to normal appearance of villi and surface epithelium. Figs. 11 to 14 from Case 1 illustrate a lesser degree of improvement of the villi, despite good clinical improvement, strict dietary regime and normal absorption; initial changes were of the severe type (+++++) with complete absence of villi and gross alteration of surface epithelial cells.

Discussion

Histological changes in the duodenal mucosa of patients with coeliac disease investigated in this study appear to be identical with those recorded by Sakula and Shiner (1957) and Rubin *et al.* (1960a). The variation in severity of the changes in the initial biopsy specimens parallels closely that observed by Rubin *et al.* (1960b) and the present findings agree with theirs, in that little correlation occurs between the severity of the lesion and the clinical symptoms; somewhat more correlation occurs with the degree of malabsorption; the closest degree of correlation is with the age of the patient. The most severe lesions occurred in the older children although again there were exceptions.

Changes in the mucosa of the small intestine in patients with coeliac disease and idiopathic steatorrhoea indicate a reduction in surface area exposed to digested foodstuffs and this is thought to be responsible for malabsorption. In the present study some of the patients with severe degree of malabsorption, as determined by fat balance, did show the most severe changes in histology of the duodenal mucosa. However, some of the children with milder lesions showed considerable malabsorption (Cases 12 and 15). Explanation of this is uncertain but only one biopsy

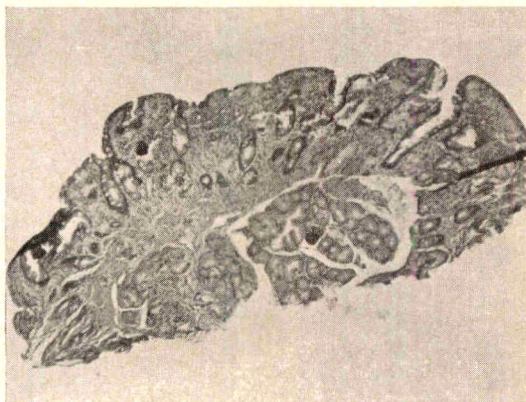
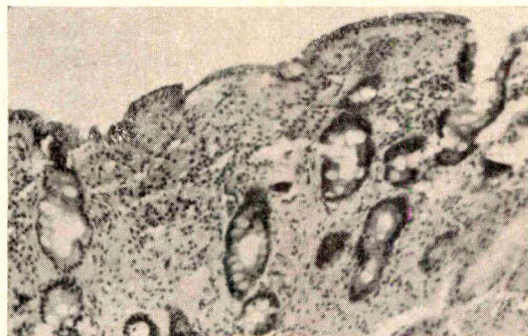
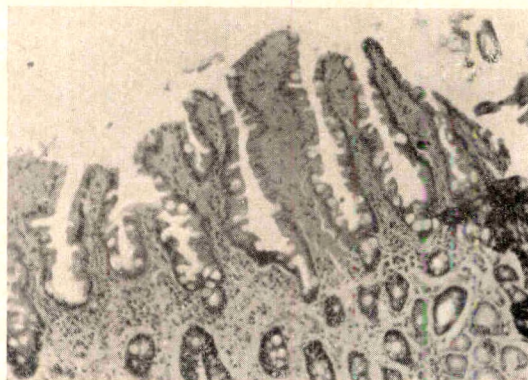
FIG. 3.—Initial biopsy ($\times 31$).FIG. 4.—Biopsy after 12 months' treatment ($\times 33$).FIG. 5.—Initial biopsy ($\times 85$).FIG. 6.—Biopsy after 12 months' treatment ($\times 86$).

FIGS. 3-6.—Case 6—illustrating improvement (+++) in duodenal biopsy specimen after 12 months' treatment with gluten-free diet. Normal appearance of villi and epithelial cells.

from each patient has been examined and the changes in the rest of the mucosa may have varied as shown by Rubin *et al.* (1960a). That clinical symptoms did not parallel biopsy changes is not so surprising since the degree of malabsorption does not always parallel severity of clinical symptoms. Observation of patients with coeliac disease during a number of years has shown that this latter finding is a common one. It is also characteristic that symptoms in later childhood may not be as severe as in early life, despite an apparently greater absorptive defect. This was clearly seen in Cases 3 and 4, two boys of 10 years, who were thought to have recovered from childhood coeliac disease and were taking a normal diet. Their absorptive defect was considerable despite only mild symptoms of recurrent abdominal pain, recurrent loose stools in one and constipation in the other. The author holds the view that the degree of malabsorption in coeliac disease does not fully explain the degree

of illness nor malnutrition and that there is probably some generalized deleterious effect of the toxic fraction of wheat gluten, this effect being more serious in the young child.

In the present series mucosal changes in the biopsies obtained during the patient's treatment with a wheat gluten-free diet have altered, and a more normal and sometimes quite normal appearance is resumed. The improvement is consistent in type although variable in degree. This finding is at variance with that of Sakula and Shiner (1957), who report one case of coeliac disease, stating that improvement in mucosal histology did not occur after five weeks' treatment. However, they give no detail of the rigidity of the gluten-free diet, nor the state of absorption at the time of the second biopsy. Rubin *et al.* (1960b), in their most recent communication, report two patients in whom they considered some improvement had taken place on a gluten-free regime, although they did not

FIG. 7.—Initial biopsy ($\times 31$).FIG. 8.—Biopsy after three months' treatment ($\times 29$).FIG. 9.—Initial biopsy ($\times 86$).FIG. 10.—Biopsy after three months' treatment ($\times 86$).

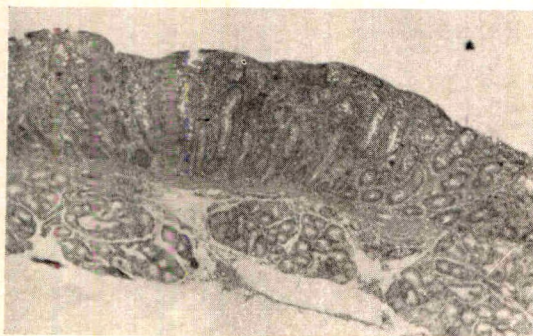
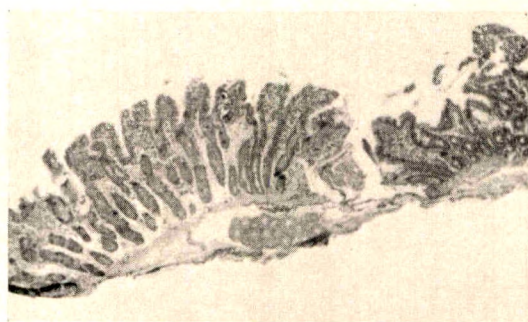
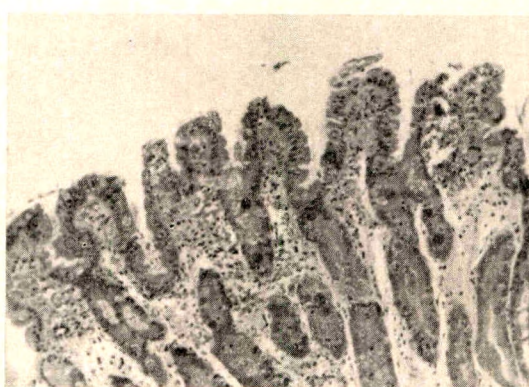
Figs. 7-10.—Case 10—illustrating improvement (+++) in duodenal biopsy specimen after three months' treatment with gluten-free diet. Normal appearance of villi and epithelial cells.

discard the view that the histological lesion was a primary one, because other patients did not show such improvement.

Single biopsies only have been examined in the present study, the state of the rest of the small intestine at the time being unknown. It is perhaps unwise to make a dogmatic conclusion from this type of material but the fact that all the patients who were followed showed some degree of improvement in histology of the mucosa is enough evidence to conclude that the lesion is at least associated with the presence of wheat gluten in the diet.

The degree of improvement varied considerably, some subsequent biopsies being normal, others showing moderate improvement, others still less. However, all showed a surface epithelial cell which looked normal, in that it was tall columnar with a basal nucleus. Variation showed up particularly

in the size, shape and number of villi. Interpretation of what is normal in this respect is difficult, as mentioned by Shiner and Doniach (1960) and observed by ourselves in controls. The fact that there can therefore be considerable variation in size, shape and number of villi in patients with normal intestinal absorption makes it not impossible that some coeliac patients may have normal or near normal absorption without completely normal villi. Moreover, in man, the small intestine is certainly longer than is necessary for maximal absorption, since considerable lengths may be removed surgically without altering absorptive capacity. Consequently a complete return to normality in histological appearances of the duodenum is not necessary before the child can be clinically well and show normal absorption. The degree of improvement may be sufficient, or other

FIG. 11.—Initial biopsy ($\times 28$).FIG. 12.—Biopsy after nine months' treatment ($\times 28$).FIG. 13.—Initial biopsy ($\times 86$).FIG. 14.—Biopsy after nine months' treatment ($\times 86$).

FIGS. 11–14.—Case 1—example of most severe changes (++++ in initial duodenal biopsy specimen, and moderate (++) improvement after nine months' treatment with a gluten-free diet. Villi still short and stumpy—epithelial cells normal.

parts of the gut may have improved still more.

If the abnormal changes are directly associated with the presence of gluten in the diet, return to complete normality must also depend on the rigidity and persistence of the gluten-free dietary regime. Experience over a number of years has shown how difficult it is for active toddlers and school children to be accurately restricted in diet. The complexity and diversity of modern, prepared and tinned foods makes it difficult for a mother to know which foods contain gluten, often used as an additive. Until the toxic fraction of wheat gluten is recognized it will not be clearly known whether small amounts may occur in other foodstuffs, in amounts, for instance, too small to cause clinical symptoms but enough to prevent full normality of the mucosa. Rubin *et al.* (1960b) did not comment on the strictness of the diet in their patients who did not show improvement in duodenal histology, but it is perhaps signi-

ficant that in the two patients who did show improvement, biopsies were obtained after only short periods of treatment. It is well known to those who treat these children that the diet is much more rigidly adhered to in the early stages of treatment than later when the child is well. The present study shows that improvement in histological appearances is evident quite early during treatment, even after only three months, at which time it may be as marked as after nine months.

From the data presented in this paper it can be seen that in very young coeliac patients who were kept as rigidly as possible to a wheat gluten-free dietary regime, the histological appearances of the duodenal mucosa improved significantly. Improvement was also noted in 6-year-old children who had had symptoms since toddler age. The two 10-year-old boys have not yet been re-investigated. The appearance of the mucosa in these older patients resembles the severity of change seen

in adult patients. It is well known that adult patients do not show such a quick response clinically to a gluten-free dietary regime as do young children (French, Hawkins and Smith, 1957). This may have some relationship to the fact that Rubin *et al.* (1960b) do not demonstrate significant improvement in biopsy specimens from older patients. Have the changes been present too long for much improvement in structure to take place, or will it take longer, or depend on the replacement of other long-standing deficiencies in these patients?

Interpretation of the mechanism of the deleterious effect of gluten on the duodenal mucosa is still a matter for conjecture and no real evidence for this is presented in this paper. Present theories of the toxic mechanism of gluten in coeliac disease postulate the production of a harmful peptide in the intestine due to incomplete proteolytic digestion of gluten (Weijers and Kamer, 1955; Frazer 1956; Alvey, Anderson and Freeman, 1957). If this is so, is this peptide directly irritative to the mucosal surface or is it absorbed, exerting its toxic influence generally on the patient and more particularly on the intestinal mucosa. Anderson, Astley, French and Gerrard (1952a) have shown from barium studies that the small intestine in coeliac disease is dilated and lacks the normal fine feathery patterning of the mucosa. They have suggested that this may be evidence of generalized loss of tone in the gut wall or that the muscularis mucosae is hypotonic. The dilatation disappears on recovery and reappears during relapse. It is well known that the young child with coeliac disease shows hypotonia of skeletal musculature out of proportion to the degree of malnutrition and that the child is temperamentally depressed. These features also disappear with treatment. It is possible that the harmful fraction of gluten may in some way cause hypotonia and that the effect of this on the gut is to depress the activity of smooth muscle and muscularis mucosae, perhaps altering the appearance of villi and mucosa. Verzar and McDougall (1936) have described and recorded the movements of the villi and their control by the muscularis mucosae. Johnson (1913) has shown, in animals, that when the small intestine is dilated the villi become shorter and blunter, the surface flatter and that alterations appear in the tall columnar cells. Is there villous atrophy as described by Shiner and Doniach (1960) or failure of formation of villi by alteration of villous mechanics?

It is possible that toxic influences other than gluten may produce similar changes in the gut and mucosa. Clinically and biochemically tropical sprue closely resembles adult idiopathic steatorrhoea

and coeliac disease, but does not respond to a gluten-free dietary regime (French, *et al.*, 1957). Butterworth and Perez-Santiago (1958) among others, have reported similar changes in the intestinal mucosa in patients with tropical sprue but these are milder in nature, resembling the less severe cases in the present series, and they are apparently reversible. The gut in this condition also has the same dilated hypotonic appearance (Ardran, French and Mucklow, 1950). Shiner and Doniach (1960) have reported similar mild reversible changes in biopsy specimens from patients with post-gastrectomy steatorrhoea. Rubin *et al.* (1960a) show good evidence that this mucosal lesion is specific to coeliac disease and adult idiopathic steatorrhoea among the series of patients they investigated. The present study shows no evidence for or against the specificity of this lesion owing to inadequacy of material. However, biopsy material from children with other disturbances of gastrointestinal function and motility, temporary as well as chronic, with or without associated malabsorption, must be studied before the specificity of this lesion, particularly in its milder grades, is unquestioned.

Summary

Histological changes in the duodenal mucosa in biopsy material obtained from 17 patients with newly-diagnosed coeliac disease are described. These changes are of a consistent pattern but vary in severity.

The abnormal changes disappeared completely or partially in biopsy specimens obtained from all 11 of these children who were followed during their first year of treatment with a diet free from wheat gluten.

The histological changes in the intestinal mucosa of patients with coeliac disease are considered to be directly associated with the ingestion of wheat gluten.

The histopathology of the lesion is briefly discussed.

Many people have helped in various phases of this work and to them I owe thanks: Dr. Rubin and his colleagues in Seattle for supplying me with an early model of the biopsy tube and personal instruction in the preparation of sections; the physicians of the Royal Children's Hospital for generously referring clinical material; the registrars, nursing staff and radiology staff who have helped in obtaining the biopsies; Miss Mavis Freeman and the Clinical Research Unit laboratory for the laboratory investigations; Miss Jean Allan for supervising the diets; the Pathology Department technicians for cutting and staining the sections; and lastly to the two pathologists, Dr. A. Williams and Dr. L. Taft, for reviewing the sections with me.

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Addendum

Since this paper has been sent to the press, Rubin, Brandborg, Flick, Parmentier, Phelps and Van Niel (1960) have demonstrated in two treated adult sprue patients that instillation of wheat into the ileum was followed by changes in the mucosa. These changes were those characteristic of the sprue lesion prior to treatment with a gluten-free diet. These authors state that this demonstration of intestinal mucosal damage by wheat implicates gluten exposure as the precursor to anatomic changes in idiopathic sprue.

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THE VALUE OF GALACTOSE PHOSPHATE DETERMINATIONS IN THE TREATMENT OF GALACTOSAEMIA

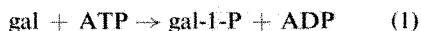
BY

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Hereditary galactosaemia is now known to be due to the deficiency of a single enzyme, galactose-1-phosphate uridyl transferase* (Kalckar, Anderson and Isselbacher, 1956). This enzyme, the second in the chain of three enzymes concerned with the metabolism of galactose, catalyses the conversion of gal-1-P to G-1-P, as shown in equation (2):



The block in galactose metabolism at step (2) would be expected to lead to an accumulation of gal-1-P when galactosaemic individuals ingest galactose. An accumulation of this phosphate has been demonstrated in the erythrocytes of untreated infants suffering from galactosaemia, or in the erythrocytes of treated cases after incubation with galactose *in vitro* (Schwarz, Golberg, Komrower and Holzel, 1956; Kalckar *et al.*, 1956). A diagnostic test for galactosaemia, based on this observation, has been reported previously (Schwarz, Holzel and Komrower, 1958).

The intracellular accumulation of gal-1-P appears to lead to a serious disturbance of erythrocyte metabolism, as indicated by a fall in the respiratory rate and by a general derangement of phosphate metabolism (Schwarz *et al.*, 1956; Komrower, Schwarz, Holzel and Golberg, 1956; Penington and Prankerd, 1958). An analogous disturbance has been demonstrated in a mutant of *E. coli* deficient in uridyltransferase: on incubation of the culture with galactose, it evinces a prolonged lag phase before the onset of growth, which is preceded by intracellular accumulation of gal-1-P (Kurahashi

and Wahba, 1958). Recently evidence has been presented which indicates that gal-1-P may exert an inhibitory effect on a number of enzymes—phosphoglucomutase, G-6-P phosphatase and dehydrogenase (Sidbury, 1957; Ginsburg and Newfeld, 1957; Lerman, 1960).

So far gal-1-P has been demonstrated only in the erythrocytes of galactosaemic infants. The liver, being the main site at which galactose is normally metabolized, would be expected to show a similar, or even greater, accumulation of this phosphate. Theoretically, all cells of the body are endowed, to a greater or lesser extent, with all enzymes and a hereditary deficiency in one enzyme might therefore make itself felt in all tissues.

The purpose of this communication is threefold: to demonstrate that gal-1-P does, in fact, accumulate in several, if not all, tissues; to draw attention to the value of assessing erythrocyte gal-1-P at regular intervals as a guide to the adequacy of treatment; to present an improved method for the determination of gal-1-P.

The gal-1-P values reported below were obtained by the method published previously (Schwarz *et al.*, 1958). Since this method was evolved and most of the determinations made, pure gal-1-P has become available, thus permitting an assessment of the efficiency of its determination. Recent experiments have shown that the original method may involve losses of galactose resulting from irreversible adsorption on, or entrainment in, the salts left after evaporation to dryness. To overcome this defect as far as possible, and still retain the specificity of the method accruing from chromatographic separation of galactose from other carbohydrate or reducing substances, the following method has been devised.

Determination of Gal-1-P

Heparinized venous blood (about 2 ml.) which may be kept in ice (not frozen) for a few hours, is centrifuged

* The following abbreviations will be used: Galactose-1-Phosphate, gal-1-P; Glucose-1-phosphate, G-1-P; adenosine triphosphate and diphosphate, ATP and ADP; uridinediphosphoglucose or —galactose UDPG and UDPgal.

in a conical graduated tube to separate the cells. After washing the cells with three changes of 10 ml. saline, the cell volume is noted.

The cells are lysed by shaking with two volumes of water and a little saponin, and by freezing. To the partially thawed haemolysate three cell volumes of ice-cold 20% trichloroacetic acid are added: the mixture is shaken well and kept exactly six minutes in an ice bath, with occasional shaking; it is centrifuged for two minutes in ice-cold buckets and the supernatant is immediately poured through a sintered glass filter.

The filtrate, whose volume is measured, is transferred to a 15 cm. glass stoppered tube, containing three drops of 25% barium acetate, one drop of phenolphthalein solution and 5 ml. ethanol, previously cooled in ice. A slight excess of 40% KOH is added. It is important to carry out these operations quickly and to keep the mixture cold while the pH is acid, since the gal-1-P is easily hydrolysed in acid solution. The ice-cold mixture is acidified with the minimum amount of acid and then basified to a faint pink with 0.1N KOH. This solution is treated with four volumes of ethanol, re-neutralized if necessary, and kept in the refrigerator for at least two hours (or over night).

The precipitated barium phosphates are spun down and the supernatant is rejected.

Ice-cold neutralized 80% ethanol (10 ml.) is added and the precipitate is suspended by swirling the tube and then allowed to settle in the refrigerator for one hour. After centrifugation the supernatant is again rejected.

The residue is treated with 1.5 ml. 0.1N HCl and the mixture is immersed in boiling water and shaken to disperse the precipitate. The tube is stoppered (spring loaded) and immersed in boiling water for 15 minutes.

After cooling, the tube is centrifuged briefly and the hydrolysate is de-ionized as follows: it is transferred to a tube (10 × 1.5 cm.) containing 0.2 g. of Amberlite Monobed resin MB-1 (analytical grade), previously washed with several changes of boiled distilled water. The mixture is shaken mechanically for 15 minutes, keeping the resin as far as possible near the bottom of the tube. After a brief centrifugation the solution is transferred with a fine-tipped Pasteur pipette, reaching to the bottom of the tube, to a 5 ml. volumetric flask. The boiling tube is rinsed three times with 1 ml. of water, the separate rinsings being used to extract the resin for five minutes each time. The solution is transferred to the flask and the volume is finally made up to the mark.

Two aliquots of 2 ml. are transferred to evaporating cups, made by cutting off test tubes of 1.3 cm. diameter about 2.5 cm. from the bottom. The solutions are evaporated to dryness in a vacuum desiccator.

One of the cups is rinsed round with five or six portions of 50% methanol to dissolve the galactose and transfer it quantitatively to the starting line of a descending chromatogram. This is run on a sheet of no. 1 Whatman paper, 58 cm. long, with a 10 cm. long folded strip of paper stapled to the bottom. Known amounts of galactose (5-50 µg.) are placed alongside the sample. After 30 minutes' equilibration the chromatogram is run for

16 to 20 hours in ethyl acetate-pyridine-water (70 : 25 : 20 by vol.) at 27° C.

After drying at room temperature, the chromatogram is dipped in freshly prepared benzidine reagent (0.5 g. of decolorized benzidine in 5 ml. glacial acetic acid and 20 ml. acetone, to which 4 ml. 100% trichloroacetic acid and acetone to 100 ml. is added) (Harris and MacWilliam, 1954). The chromatogram is heated for two to four minutes in an oven at 100° C. until the paper begins to turn pale yellow.

The amount of galactose in the aliquot used for chromatography is estimated visually by comparison with known amounts, either in daylight or in ultra-violet light, taking into account both the yellow colour (daylight) or greenish yellow fluorescence (u.v.) given by 0.2-10 µg. quantities of galactose, and the brown centres (non-fluorescent) given by larger amounts. The other aliquot of the de-ionized dried hydrolysate is available, if necessary, for making a closer assessment of the galactose content on the basis of the first result.

Results Obtained by the Improved Method. In four experiments in which pure gal-1-P had been added to a normal haemolysate and glucose-1-C¹⁴ to the hydrolysate, the recoveries were as shown in Table 1. It can be seen from this Table that about 90% of the labelled glucose has been recovered. The loss of about 10% of the glucose (probably due to irreversible adsorption on the resin) is, presumably, paralleled by a similar loss of galactose. A recovery of 90% is thus the best of which the method is capable. The maximum error involved in the visual assessment of galactose on the chromatogram is of the order of 10%. The over-all accuracy of this method can be considered adequate for the purpose of routine checks of erythrocyte gal-1-P levels.

TABLE 1
PERCENTAGE RECOVERY OF ADDED GAL-1-P FROM
HAEMOLYSATE

Experiment	Glucose-1-C ¹⁴	Gal-1-P
1	93.1	100
2	90.2	92
3	91.2	84
4	88.8	100

Untreated Cases

Table 2 shows the gal-1-P levels found in untreated cases, aged 10-28 days, and in a patient of 4½ months after eight days on a milk diet. (The results reported below were obtained by the original method of Schwarz *et al.* (1956) as indicated in the introduction and are liable to be somewhat too low.)

With the exception of L.B. (whose clinical record was not available), the values are between 300 and 400 µg./ml., irrespective of age. This suggests that the galactose phosphate level may tend to a maximum attained after prolonged exposure of the cells to galactose.

TABLE 2
GAL-1-P IN UNTREATED CASES

Patient	Age	Gal-1-P ($\mu\text{g./ml. cells}$)
Susan B.	1½ weeks	360
S.B.	3 weeks	330
M.C.	4 weeks	300
L.B.	3 weeks(?)	130
A.J.	4½ months	400

Effect of Treatment

Fig. 1 shows the rate of progress of three infants. One of these (B.J.) was diagnosed at three days and was fed no milk from birth. Her cord blood contained 50 $\mu\text{g. gal-1-P/ml. cells}$, which must have been formed *in utero*.

After treatment for varying periods, the level of intracellular gal-1-P presumably depends on the galactose content of the diet. The scatter diagram (Fig. 2) shows the values obtained in 36 determinations on 13 patients and five normals. It can be seen that normal values are substantially less than the lowest found in treated galactosaemic infants.

Gal-1-P in Other Tissues

Organs from two infants who died from galactosaemia before the diagnosis could be made, were obtained at necropsy. In one case (M.C.) the material did not become available for analysis until several days after necropsy, having been left at room temperature in the meantime. The gal-1-P levels are, therefore, of no more than qualitative significance. The results are shown in Table 3, from which it is clear that gal-1-P might reasonably be expected to accumulate in all tissues of the body.

A biopsy specimen of liver taken at laparotomy from a patient in whom haemolytic disease of the newborn as well as other complicating factors were present in addition to galactosaemia, contained 50 $\mu\text{g. gal-1-P/g.}$ after four months of treatment. The galactose phosphate level in the erythrocytes

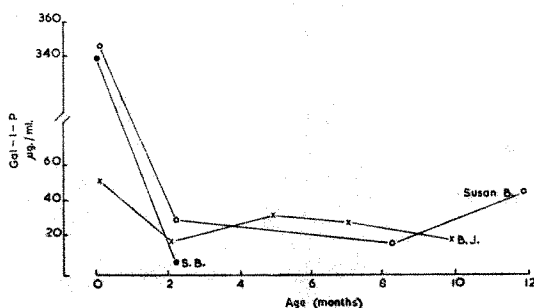


FIG. 1.—Change in gal-1-P levels during treatment.

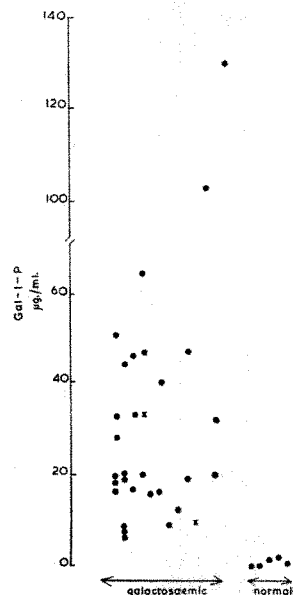


FIG. 2.—Erythrocyte gal-1-P in treated patients. $\times$ indicates blood analysed shortly after exchange transfusion, hence low gal-1-P levels do not reflect adequate treatment.

TABLE 3
GAL-1-P IN ORGANS

Organ	Patient M.C. ($\mu\text{g./g.}$)	Patient L.C. ($\mu\text{g./g.}$)
Whole blood	—	270
Liver	20	90, 75*
Kidney	3	145
Brain	0	65, 69*
Tongue	—	87
Adrenal	4	—
Heart	20	—
Gallstones	22	—

was estimated at the same time and found to be 64 $\mu\text{g./ml.}$

Discussion

There is now considerable evidence that gal-1-P, by interfering with the normal metabolism of the cell, may be responsible for the clinical manifestations of galactosaemia. The demonstration that the phosphate accumulates in a variety of tissues of the galactosaemic infant if his diet contains galactose, is in line with the diversity of the symptoms. Even if all tissues are liable to suffer damage from the accumulation of the 'toxic' phosphate, in some the existence of sufficient functional reserve would prevent this damage from manifesting itself clinically.

It may be mentioned here that Schwarz and Golberg (1955) showed that the lens capsules and epithelia of rats suffering from galactose cataract

contained approximately 170 $\mu\text{g. gal-1-P/g.}$, whereas non-cataractous lenses of galactose-fed animals contained not more than 0.1 of this amount. Recently, Lerman (1960) has shown that an inhibition of lenticular G-6-P dehydrogenase and of glucose catabolism is demonstrable two to four days after instituting a high galactose diet, and that the ATP content of the tissues drops to very low levels. This interference with normal metabolism might well result from the accumulation of gal-1-P and probably accounts for the gradual opacification.

If one accepts the premise of the 'toxic' nature of galactose phosphate, the question arises at what concentration this substance begins to exert its deleterious effect on cellular metabolism. Unfortunately, it is not yet possible to offer an answer, since it is difficult to simulate intracellular conditions *in vitro*. In erythrocytes a gal-1-P concentration of 150 $\mu\text{g./ml.}$ was found to inhibit cellular respiration by 30% (Schwarz *et al.*, 1956), but other, metabolically more active, cells might be more or less affected by such levels. It was pointed out, in connexion with Table 2, that in untreated cases the galactose phosphate concentration rises to what appears to be a maximum of 300-400 $\mu\text{g./ml.}$ Since this level would be reached quite rapidly (12-16 hours, in the presence of sufficient galactose to saturate the enzyme) (Kalckar *et al.*, 1956), it seems that the accumulation of the phosphate is self-limiting, i.e. analogous to the well-known product inhibition of hexokinase.

Since it is not known what constitutes a 'safe' level of intracellular galactose phosphate and since both its rate of formation and its rate of removal may be different in each tissue, the determination of galactose phosphate in erythrocytes can probably furnish no more than an indication of whether the general tissue level is rising or falling. On the single occasion when a biopsy specimen of liver could be examined, the galactose phosphate level was close to that in the erythrocytes, but in the necropsy specimens the levels differed considerably.

The presence of a fairly substantial amount of gal-1-P in the cord blood of a galactosaemic infant raises the question of the mother's diet during pregnancy. In the case recorded no galactose could be detected chromatographically (i.e. less than 5 mg. %) in the mother's venous blood on two occasions after the consumption of one pint of milk. From this one may infer that the galactose phosphate had accumulated in the foetal tissues by prolonged exposure to small amounts of galactose transferred across the placenta.

From the results presented in this paper and from clinical findings reported previously (Komrower

et al., 1956), it is clear that, ideally, the galactosaemic infant should be provided with a completely galactose-free diet. In practice such treatment is fraught with difficulties due both to the wide distribution of galactose and to the degree of conscientiousness required on the part of the mother. It should be emphasized here that many foods contain galactose in the form of α -galactosides (lactose is a β -galactoside) which may not be hydrolysed to free galactose in the intestinal tract. But until it is known for certain that no galactose is liberated either by the digestive enzymes or by the intestinal flora, foods containing α -galactosides should be avoided (Schwarz, Holzel, Stapleton and Goodell, 1959).

In view of the practical difficulties associated with the diet, regular assessment of the gal-1-P level in the erythrocytes constitutes a ready, and indeed the only, means of checking the adequacy of the diet, from the point of view of exclusion of galactose. The disappearance of frank symptoms is probably not a reliable indication that treatment is adequate and successful, especially as the developing nervous system may be more sensitive than other tissues to a slight but persistent interference with normal metabolism.

Final judgment on the effect of ingesting small amounts of galactose and consequent accumulation of the phosphate in the tissues has to be deferred until more information is available on the maximum level which can build up in the cell without interfering with metabolism. It is, however, well to consider that a uniform distribution of gal-1-P in the total intracellular water corresponding to a level of 150 $\mu\text{g./ml.}$ erythrocytes, which is known to affect erythrocyte metabolism, would be equivalent to about 400 mg. of galactose for a 7 kg. infant. Since a much lower concentration of the phosphate might turn out to be damaging, it will be appreciated that the amount of galactose involved is quite small. Thus, a 'low lactose' milk, claimed by the manufacturers to contain, in the reconstituted condition, not more than 0.012% galactose, i.e. equivalent to 400 mg. in 3½ litres., would supply what might be a highly toxic dose in a few days.

It should, however, be emphasized that apart from the gaps in our knowledge of the degree of toxicity of gal-1-P and of the rate of accumulation in different tissues, there is bound to be a considerable variation from one individual to another, due to the variability of such factors as rate of absorption, renal efficiency and, above all, a residual capacity to metabolize galactose by the usual or an alternative pathway (Isselbacher, 1957). In consequence it is impossible to dogmatize on the

precise significance of particular galactose phosphate levels. Until the gaps in our understanding are closed, a cautious approach is indicated.

Summary

Hereditary galactosaemia is characterized by a deficiency of the enzyme galactose phosphate uridylyltransferase, which catalyses the conversion of galactose-1-phosphate to glucose-1-phosphate. The deficiency leads to an intracellular accumulation of gal-1-P when the patient's diet contains galactose. There is evidence indicating that this phosphate inhibits a number of enzymes and that by these, or other, means it interferes with normal cellular metabolism.

Analysis of necropsy material has shown that galactose phosphate is deposited in several, if not all, tissues, thus probably accounting for the diverse ill-effects constituting the galactosaemic syndrome. The determination of gal-1-P in the erythrocytes affords a ready means of assessing the adequacy of treatment, of which the disappearance of frank symptoms is an insufficient guide. The amounts of galactose potentially capable of damaging cellular metabolism are quite small. This fact and the wide distribution of galactose impose a heavy burden on the galactosaemic patient's mother and clinician alike, thus rendering a regular check by galactose phosphate determination desirable.

An improved method for the estimation of galactose phosphate in erythrocytes is presented.

I would like to thank the many paediatricians who have referred their patients to me and have given their permission to incorporate the results in the scatter diagram. I wish to express my appreciation for the supply of necropsy material by Dr. L. L. R. White and Dr. J. L. Emery. I am indebted to Professor W. Gaisford and Dr. A. H. Gowenlock for valuable discussion. The analyses and much of the development work were carried out by Miss Naomi Simpson, whose skill and patience it is a pleasure to record.

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TREATMENT OF ENCEPHALOTRIGEMINAL ANGIOMATOSIS (STURGE-WEBER DISEASE) BY HEMISPHERECTOMY

BY

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Encephalotrigeminal angiomas or Sturge-Weber's disease is an uncommon congenital disorder which can vary greatly in the extent of its manifestations, but which in severe cases can lead to infantile hemiplegia associated with fits, behavioural disorders and mental backwardness. Until comparatively recently specific therapy was largely limited to anticonvulsant drugs. Only a few isolated reports of surgical intervention have been recorded. The purpose of this paper therefore is to describe the findings and results of surgery in five consecutive patients with infantile hemiplegia treated by hemispherectomy and since followed up for from three to eight years who improved as regards epilepsy and personality disorders, although not as regards hemiplegia. A preliminary report on the first two of these cases has already been presented (Polani, 1952).

Excellent reviews of the clinical manifestations and pathogenesis of the condition have recently been given by several authors (Medoc, Sotelo, Arana Iñiguez and Estable Puig, 1953-1954; Lichtenstein, 1954; Wollwill and Yakovlev, 1957; Norman, 1958; Peterman, Hayles, Dockerty and Love, 1958). The essential lesion appears to be a venous angiomas of the leptomeninges generally over one cerebral hemisphere, most often in the posterior parietal and occipital regions, associated with a port-wine naevus of the skin of the face in the territory of one or more divisions of the trigeminal nerve, on the same side of the body. Occasionally both cerebral hemispheres are involved, and the cutaneous naevus may also be in other parts of the body. In all cases the affected areas of cortex become atrophic with the deposition of calcium and ferruginous materials that give rise to a characteristic curvilinear appearance on radiographs. Other lesions that may be present include angioma of the choroid of the eye and ipsilateral buphthalmos or glaucoma. Dural and diploic vascularity is exceptional.

The first recorded case description is that of

Rudolf Schirmer (1860) who described a 36-year-old patient with an extensive naevus involving both sides of the face, left more than right, as well as the chest and abdomen. He did not mention any neurological features, but pointed out that the patient's left eye protruded, and that there was hydrophthalmos and varicosities of the retinal veins. Allan Sturge (1879) demonstrated to the Clinical Society of London a girl of 6½ years of age who had an extensive 'port-wine mark' over the right side of the head and face with enlargement of the right eye and vascular changes in the choroid. He inferred that her left-sided fits were caused by a similar vascular lesion of the right side of the brain. Kalischer (1897) gave the first autopsy report of this condition. He (1897; 1901) described an extensive telangiectasis of the scalp and the surface of the brain, all on the same side. He did not, however, observe any calcification, presumably because his subject was only 1½ years old. Hebold (1913) was the first to note the cerebral calcification, but did not determine its precise situation. However, Weber (1922; 1929) was the first to publish a radiograph of the double curvilinear shadows that outline the sulcal pattern, although according to Krabbe (1934) Wissing, in 1921, had demonstrated these features to the Radiological Society of Copenhagen. It was Krabbe (1934) himself who demonstrated that the calcium deposits occurred within the cortex and not in the angiomatous vessels. Dimitri (1923), from the Argentine, also published an early description of the radiological appearances.

By this time the essential features of the disease were all recorded, but there has been some difference of opinion over nomenclature. 'Sturge-Weber disease' or 'Sturge-Weber syndrome' have become sanctioned by usage, although Weber (1936) disclaimed the use of his name and suggested that it be called 'Sturge-Kalischer disease'. It has also been called 'Krabbe's disease', and 'Sturge-Weber-Dimitri disease' (Lichtenstein, 1954), and 'Sturge-Weber-Krabbe's disease' (Krayenbühl, Yaşargil and

Uehlinger, 1957). Of the non-eponymous terms 'encephalotrigeminal angiomatosis' or 'meningo-facial angiomatosis' seem the most accurate. In making the diagnosis it must be remembered that, like most congenital malformations, the syndrome may be incomplete. It is therefore advisable to limit the definition of Sturge-Weber disease to cases showing at least two of the major signs, such as facial naevus combined with either intracranial angioma or with angioma of the choroid of the eye (Poser and Taveras, 1957; Norman, 1958). This rules out many superficially allied conditions such as spinal cord angiomas with cutaneous naevi of metamerical distribution, cutaneous naevi with cerebellar symptoms, and the familial non-calcifying meningeal angiomas (Norman, 1958), and also the cerebral calcification epilepsy of Geyelin and Penfield (1929).

Technique of Hemispherectomy in Sturge-Weber Disease

As all the cases in our series were operated upon in the same way, it will be convenient to outline the surgical technique used before proceeding to the case reports. To Krynauw (1950) must be given the credit for introducing, on a sound and systematic basis, the operation of hemispherectomy as a method of treating epilepsy and behavioural disorders in patients with infantile hemiplegia from various causes. The technique advocated by him, which has been followed by others (Cairns and Davidson, 1951; Gros, 1951; McKissock, 1953 and 1954), was to remove the cerebral hemisphere in segments. Obrador Alcalde (1950 and 1952), however, removed the affected cerebral hemisphere in one piece, and a similar technique was employed in all our cases. This technique stems from the original work of Dandy (1928), who first removed the cerebral hemisphere of a patient because of a glioma, and has since been adopted by others (Gros and Vlahovitch, 1954; French, Johnson, Brown and Van Bergen, 1955).

All our operations were performed under general anaesthesia without the use of hypothermia or of arterial hypotension. A large fronto-temporo-parietal craniotomy is turned extending medially from the midline to the floors of the anterior and middle cranial fossae laterally. The scalp incision is outlined in Fig. 5. Beneath it the bone flap is cut and pedicled on the temporal muscle. The dura is then opened in such a way that it can be sutured later. After the preliminary inspection of the hemisphere the first step in the excision is to elevate the frontal lobe and open up the inner part of the sylvian fissure so that the middle cerebral artery can be clipped and then divided just distal to its central perforating branches. This step lessens subsequent bleeding.

Attention is then turned to the region of the sagittal sinus, and the veins entering it from the superior margin of the hemisphere are coagulated and divided from before laterally. This enables the hemisphere to be retracted from the falx, exposing the mesial surface of

the opposite cerebral hemisphere, the corpus callosum and the two anterior cerebral arteries. The ipsilateral anterior cerebral artery can then be divided a little distal to the anterior communicating artery, while the ipsilateral edge of the corpus callosum is then incised from its genu anteriorly to its splenium posteriorly so exposing the interior of the lateral ventricles. Retraction of the hemisphere permits the caudate nucleus to be identified, and separation of the hemisphere from the basal ganglia and thalamus is commenced by dividing the cerebral substance along the lateral edge of the nucleus towards its tail. This cut is extended until the temporal horn is laid open. The surgeon then returns to the genu and after dividing the rostrum of the corpus callosum, he divides the frontal cortex immediately in front of the chiasm and optic nerve, so opening into the cut through which the middle cerebral artery was severed. This is then extended subpially along the infero-medial temporal border removing the uncus and hippocampus, the free edge of the tentorium being followed, and the posterior cerebral artery being severed. The penultimate stage is now reached whereby the cortex and white matter of the isthmus of the limbic lobe is divided right through from the trigone of the lateral ventricle to the tentorial opening. The last stage of removal is undertaken by dividing the veins which pass from the occipital pole to the various venous sinuses. Finally, the choroid plexus is coagulated to prevent excessive cerebrospinal fluid formation, as so much of the absorbing area has been taken away with the resected hemisphere. The dura is then closed and the cavity filled with Ringer's solution. The bone and scalp flaps are replaced.

A blood transfusion is given during the operation. Recovery is usually rapid. The only complication encountered in this series was an indolent infection in Case 1 of the large dead-space between the sutured dura and the skull. This was controlled by antibiotics and eventually cured by removing a small sequestrum that had formed at the centre of the inner table of the skull. In two hemispherectomies for infantile hemiplegia for other lesions, one of us (M.A.F.) has also encountered the complication of a communicating hydrocephalus involving the operative cavity with the ventricular system and spinal subarachnoid space. It appears to be due to the brain-stem shift described by Cabieses, Jeri and Landa (1957), and in both cases was relieved by reopening the craniotomy and dividing the tentorium cerebelli so relieving the upward thrust of the midbrain and cerebellum. This complication occurred even though the choroid plexus had been coagulated.

Removal of the cerebral hemisphere in the manner described is no more difficult than the technique employed by Krynauw, and has the advantage of procuring a specimen that is intact.

Case Reports

Case 1. R.D., $3\frac{1}{2}$ years of age, was referred by Dr. P. R. Evans. This boy was born with a left facial naevus. Seizures started at the age of 4 months, and were characterized by clonic movements of the right

limbs, and deviation of the head and eyes to the right. At first they occurred in clusters every day for a week, followed by periods of freedom of up to four months, but later, in spite of intensive medication with phenobarbitone, potassium bromide and phenytoin, they occurred several times daily. Weakness of the right arm and an extensor plantar response were first noted when he was 13 months old, but radiographs of his skull at that time were reported to be normal, although encephalography showed a shrunken left hemisphere. An arteriogram was also said to be normal. There were no temper tantrums, but he was sullen, moody and irritable.

EXAMINATION. He was small, pallid and under-developed; he was very backward, and could only utter a few words; he understood simple commands and could point out objects. The naevus was patchy and involved the ophthalmic and maxillary divisions of the territory of the left trigeminal nerve (Fig. 1). No bruit



FIG. 1.—Case 1, before operation, showing characteristic naevus which has been partially bleached by past applications of carbon dioxide snow.

was heard over the skull. The optic fundi were normal. A right homonymous hemianopia was demonstrable by menace. There was a right-sided infantile hemiplegia characterized by some wasting and shortening of the limbs with spastic weakness; this weakness was slight in the lower face. Motor power at the shoulder and elbow was reduced about 50%. He could grip feebly with his fingers, but could not extend his right wrist or fingers. The weakness was less obvious in his right leg where he could dorsiflex his ankles and move his toes. The tendon jerks were increased in right arm and leg, and the right plantar response was extensor. He responded equally to pinprick on both sides of the body. He walked with great difficulty. The left limbs were normal.

INVESTIGATIONS. Skull radiographs showed gross reduction in size of the left half of the cranial cavity, while the sulcal pattern of practically the whole of the left cerebral hemisphere (except for the frontal region) was outlined by the characteristic double-paralleled, sinuous, curvilinear lines (Figs. 2 and 3). Pneumo-encephalography showed that the ventricular system

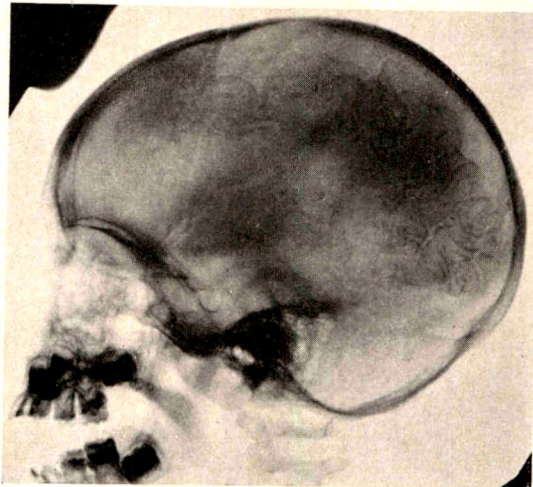


FIG. 2.—Case 1, straight lateral radiograph of skull, showing characteristic calcification.

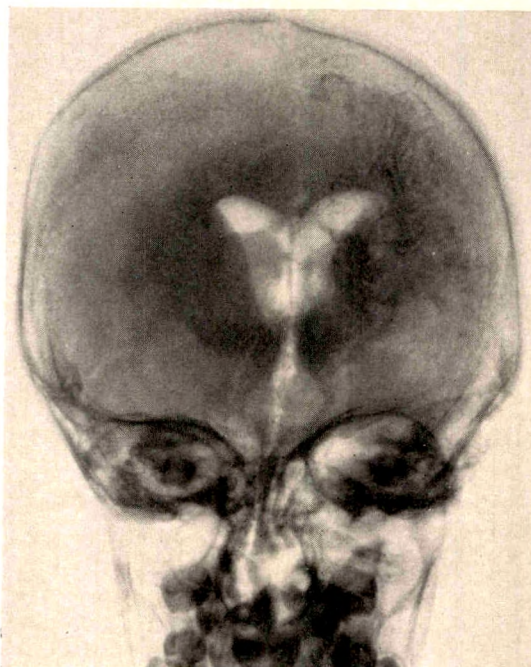


FIG. 3.—Case 1, antero-posterior air encephalogram, showing smallness of left cerebral hemisphere.

was of normal size and shape, although displaced to the left because of the atrophy of its left cerebral hemisphere. Electroencephalography disclosed greatly diminished activity over the left cerebral hemisphere without definite spiking or other epileptic activity.

OPERATION. A large left-sided craniotomy was performed on August 15, 1951, under general anaesthesia. The whole convexity as seen through the craniotomy appeared red and congested with a fine network of small blood vessels closely meshed. These tiny blood vessels were in the subarachnoid space and they, together with cerebrospinal fluid, had elevated the arachnoid off the cortex so that at first the sulcal pattern could not be discerned (Fig. 4). When, however, the arachnoid

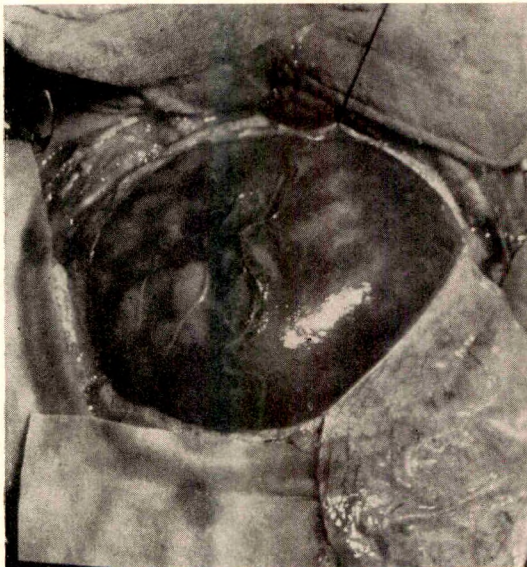


FIG. 4.—Case 1, operative appearances of left cerebral hemisphere as seen from the head of the operating table. Notice that whereas the pia-arachnoid alongside the superior longitudinal sinus is still lifted off the cortex, the convoluted pattern over the convexity of the cortex is becoming apparent as cerebrospinal fluid drains away from the sulci.

was pressed upon firmly with a glass slide, the subarachnoid spaces emptied so that one could see pale cortex between the interstices of the vascular network. The network itself did not blanch. Later this network was found to involve the whole surface of the left cerebral hemisphere on its medial and inferior aspects as well as over the convexity. The whole left hemisphere except for its thalamus and caudate nucleus was then removed in one piece. The patient stood the operation well. His immediate recovery from operation was excellent (Fig. 5), but six weeks later a low intermittent pyrexia commenced. An abscess appeared under the scalp and was controlled by aspiration and antibiotics. There remained a residual discharging sinus in the temporal fossa which did not finally heal until a small sequestrum

was removed from the inner table at the centre of the bone flap one year after the original operation.

PATHOLOGY. Photographs of the specimen after operation gave a poor impression of the vascularity of the subarachnoid network (Fig. 6), but a radiograph showed the characteristic double curvilinear lines with great clarity (Fig. 7). The specimen was preserved in the Gordon Museum, Guy's Hospital, after two blocks had been taken for histological examination. Dr. A. L. Woolf subsequently reported on these blocks as follows:

'The pia arachnoid was extremely vascular, the vessels resembling arterioles and venules, but in both cases having an unusually thick collagenous coat (Fig. 8). This coat was rich in fibroblasts. The arterioles had a well-marked muscular media. Occasionally this muscular coat was very thick indeed. Deep to the pia was a thick feltwork of glial fibres. In the cortex itself loss of nerve cells was confined to perivascular clearings, but there was much gliosis. There was no increase in microglia. There were very numerous calcospherites throughout the cortex and white matter of the occipital lobe, but an origin in calcified blood vessels could not be definitely shown. The capillaries in the cortex were increased in prominence and some had unduly thickened walls. Calcospherites were less numerous in the frontal lobe.'

PROGRESS. He has since been followed for over eight years, and has been completely free of fits and no anti-convulsant medication has been administered during that time. For the past three years he has been attending a school for physically handicapped children. He plays well with other children, and is not unduly aggressive or timid. Mentally, he is backward, but he is educable and interested in what goes on. He can read and write simple words and perform simple arithmetic, but his mental age is probably 7 years (Schonell R.; age 6 years 10 months, when actually 11 years old—D. Shalman). He has a right homonymous hemianopia. The right arm is held with the wrist flexed. He has good movements at the shoulder and a useful grip in the right hand which he uses to steady objects. The right leg is 2 cm. shorter than the left, and although the leg is generally weak, he can walk with surprisingly little limp. The degree of hemiparesis has not been altered by operation. He was reported by his school teacher to be 'sociable and affectionate'.

Case 2. A.McK., 6 years of age, was referred by Dr. P. R. Evans. This girl was born with a port-wine stain of the left side of her face and scalp. She appeared otherwise normal until the age of 3 months when she began to have seizures involving the right side of her body. At first these were severe and frequent, lasting up to 10 minutes, and not responding noticeably to phenobarbitone. Generalized convulsions occurred at times. In her first two years of life she also had six separate attacks of pneumonia. Investigation elsewhere by left carotid arteriography was said to be normal,

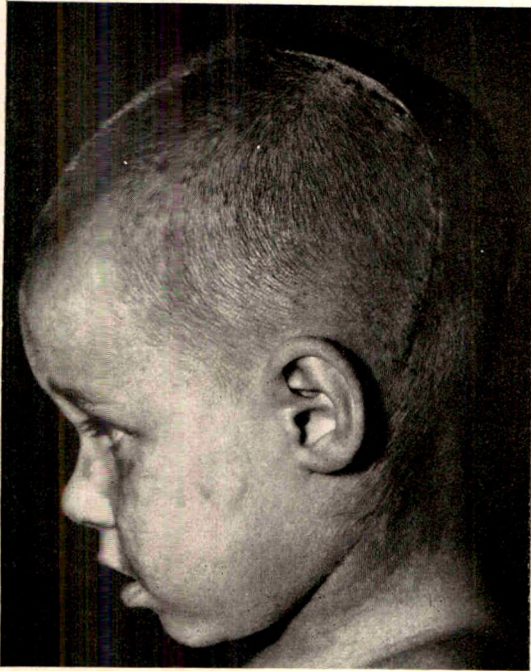


FIG. 5.—Case 1, appearances of wound 15 days after operation.

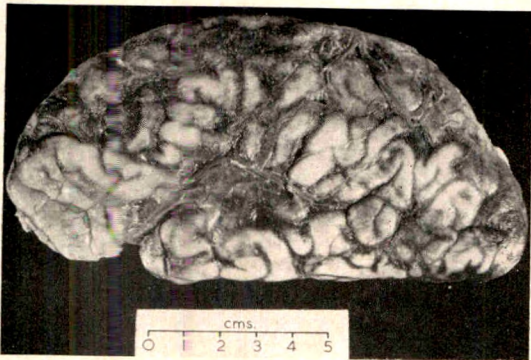


FIG. 6.—Case 1, lateral view of the resected hemisphere after excision to be contrasted with Fig. 4.

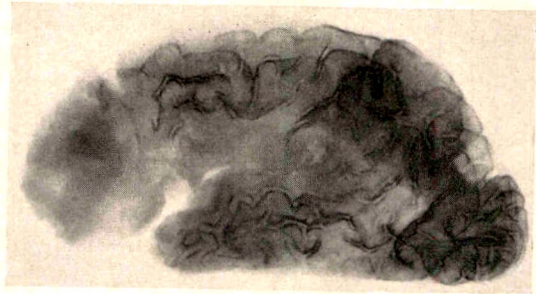


FIG. 7.—Case 1, radiograph of resected specimen after removal of two blocks for histological examination.



FIG. 8.—Case 1, photomicrograph showing numerous abnormal arterioles and venules in leptomeninges and also in outer layers of cortex. Cresyl violet $\times 41$.

while pneumoencephalography showed gross atrophy of the left cerebral hemisphere. There was no mention of cerebral calcification. By the age of 18 months it was evident that her right limbs were weak and spastic, and by the age of 6 years her fits had become milder and would often only involve the right limbs without loss of consciousness. However, she would then average two to three attacks per week in spite of sedation with various

anticonvulsant drugs. She did not talk until she was 2 years old, nor walk until she was 4 years. At 6 years she could say only a few simple words, and recognize and sing simple nursery tunes. Her behaviour had recently begun to deteriorate. She would fly into tempers if thwarted or disappointed, and in these tantrums she would scream, stamp and throw things around for periods of up to half an hour.

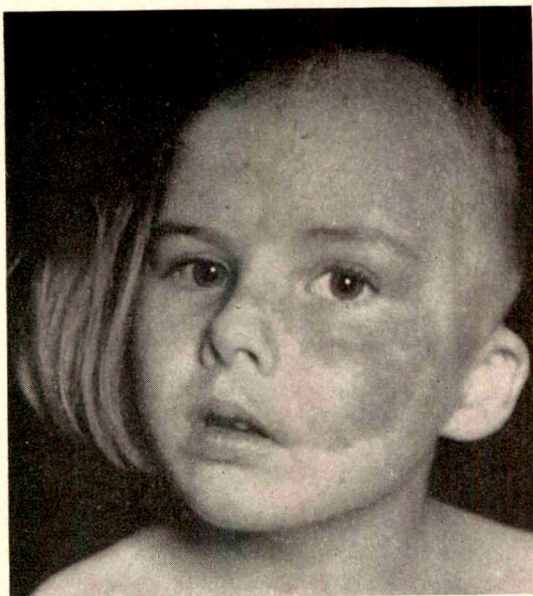


FIG. 9.—Case 2, photographed 15 days after operation to show extent of naevus as well as the scalp incision.

EXAMINATION. She was thin and undersized. The telangectasis involved the left side of her face in the distribution of the upper two divisions of the trigeminal nerve (Fig. 9). She spoke in simple words and was not dysphasic. Her mental age was between 2 and 3 years (E. Norman). Her optic fundi were normal, but she

showed a right homonymous hemianopia. There was an inconstant divergent strabismus. The right lower face was weak. The right arm was somewhat wasted and spastic, and about 3 cm. shorter than the left. It was held flexed at the elbow, forearm hyperpronated, and with wrist and fingers flexed. Proximal movements were better preserved than distal, and she could abduct the shoulder against gravity, but her hand grip was feeble. The right leg was 4 cm. shorter than the left with a spastic talipes equino-varus deformity. Muscle power was greatly diminished in all groups, but she could walk and even run unassisted although with a limp. She reacted equally to pinprick on both sides of the body.

INVESTIGATIONS. These were similar to those of Case 1. Radiographs of the skull showed that the left half of the cranial cavity was smaller than the right with extensive sinuous calcification of the left hemisphere (Fig. 10). On pneumoencephalography no air entered the ventricular system, but there was an extensive accumulation of subarachnoid air on the left side. Electroencephalography under secobarbital sedation showed absence of activity over the whole of the left hemisphere. No epileptic discharges were seen.

OPERATION. This was performed on April 1, 1952. The procedure and the appearances were similar to those observed in Case 1. Immediately on recovery from the anaesthetic, the condition of the right limbs was found to be unchanged. Her postoperative recovery was straightforward.

PATHOLOGY. The macroscopic and radiographic

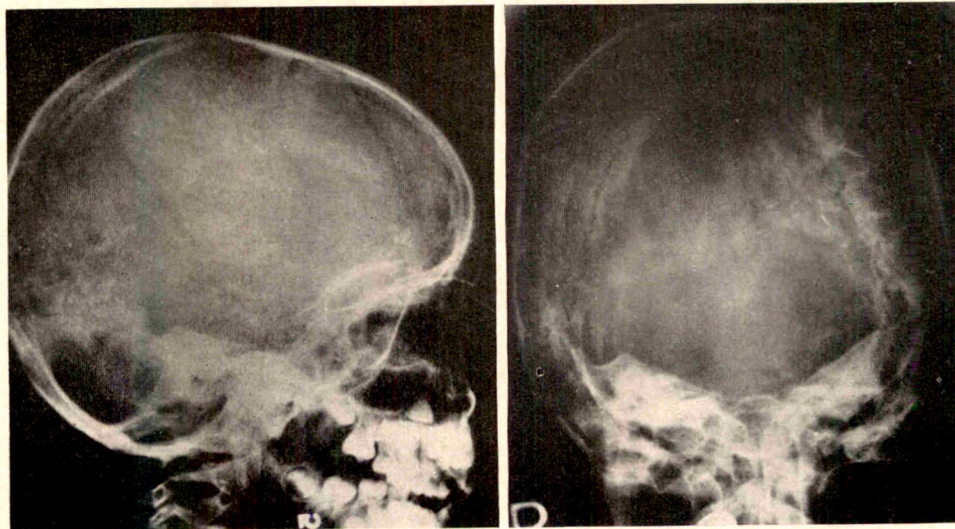


FIG. 10.—Case 2, straight radiographs showing characteristic calcification together with atrophy of left cerebral hemisphere.

appearances of the specimen were similar to Case 1. Dr. Barbara Smith reported as follows:

'The pia-arachnoid was thickened and contained a collection of abnormal vessels (Fig. 11). In the

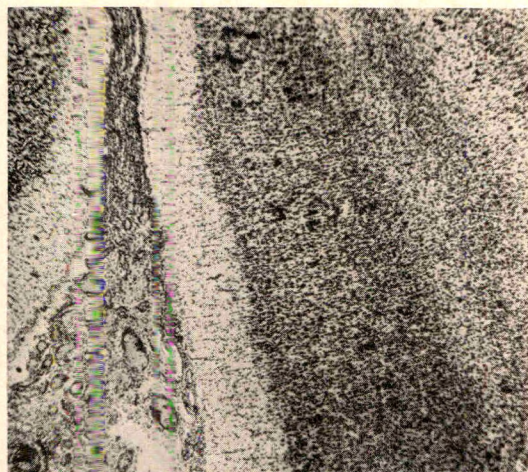


FIG. 11.—Case 2, photomicrograph showing thickened and abnormally vascular leptomeninges overlying an area of cortex which is gliotic and contains scattered calcospherites. Cresyl violet $\times 26$.

occipital block there was very marked subpial gliosis. This was less apparent in the frontal region. There were an increased number of astrocytes in the grey and white matter. Some of the pyramidal cells especially in the third layer appeared shrunken. Calcospherites were scattered throughout the cortex and white matter.'

PROGRESS. She has since been observed for seven and a half years, and during that time has been completely free of seizures. Although rather excitable, she is good at home and has no behaviour disorder. She remains, however, very backward although educable. Her mental age at 7 years 4 months on the Merrill-Palmer scale was 3 years 11 months, i.e. I.Q. 53 (E. Norman). At 13 years her mental ability as judged by reading primers, was 7 to 8 years. She attends a special school, and has participated in television performances. The hemi-aresis and hemianopia are unchanged. She can appreciate light touch and pinprick equally on both sides, but two-point discrimination and postural sensibility is grossly impaired on the right side.

Case 3. S.W., $3\frac{1}{2}$ years of age, was referred by Dr. P. R. Evans. This girl was born with a naevus of the right forehead. Starting at the age of 3 weeks, she had a series of fits in which she would become rigid and cyanosed for a few seconds. These fits kept recurring two to six times daily for a period of three weeks, and have not since recurred. When she was 12 months old it was first noticed that she was liable to burst into screaming attacks. These attacks occurred whenever

she craved attention, and once she received this she quietened down. In the tantrums she would frequently bang her head on the floor. At the age of 18 months her left limbs were first noticed to be weak, and subsequently the weakness gradually became more pronounced. She sat up at the age of 15 months, and walked at 2 years. Hemispherectomy was first considered when she was 18 months old, but as she was free of fits, it was decided to wait. However, her personality disorder and temper tantrums became so marked that she was almost unmanageable. She was, therefore, admitted at the age of $3\frac{1}{2}$ years for operation.

EXAMINATION. She was a thin, irritable girl, who could, however, be pleasant when she was allowed to have her own way. There was a naevus of the right forehead in the distribution of the ophthalmic division of the trigeminal nerve (Fig. 12). The optic fundi were normal, but there was a left homonymous hemianopia. There was also a left infantile hemiplegia of marked degree. The left limbs were a little shorter and smaller than the right. The left arm was held across the chest with the fist clenched and the elbow flexed to a right

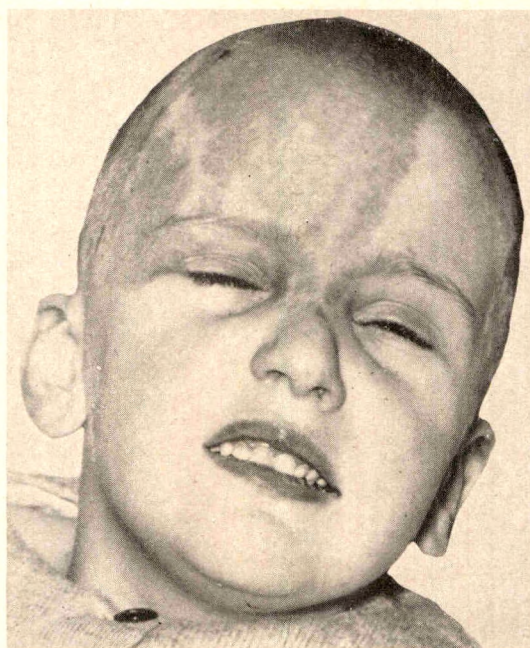


FIG. 12.—Case 3 before operation in a temper tantrum.

angle. She walked with a spastic left foot drop. Psychological testing showed that her mental age on the Merrill-Palmer scale was 2 years and her intelligence quotient was 56 (Stanford Binet Form L.—Miss M. Newell).

INVESTIGATIONS. Skull radiographs showed the right half of the cranial cavity to be smaller than the left

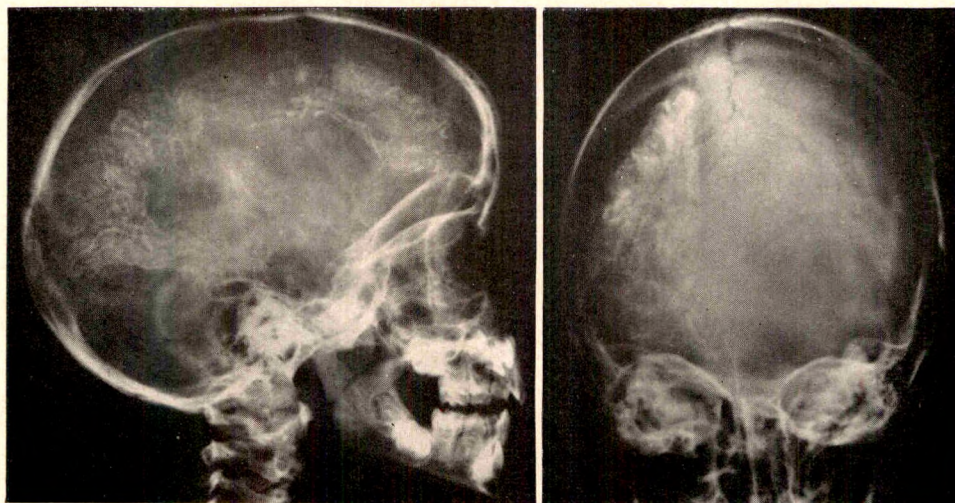


FIG. 13.—Case 3, radiographs showing characteristic calcification and right cerebral atrophy.

with extensive calcification in the right cerebral hemisphere of characteristic Sturge-Weber type (Fig. 13). A second E.E.G. record showed almost total absence of rhythmic activity over the right hemisphere with normal sleep rhythms on the left. There was no epileptic activity.



FIG. 14.—Case 3, 17 months after operation.

OPERATION. A right lateral craniotomy was performed on March 30, 1954, with similar findings to the preceding cases. The whole right cerebral hemisphere presented a typical telangiectatic blush with a fine network of venous angiomatous vessels in the leptomeninges. The right hemisphere was removed in one piece except for its basal ganglia. The postoperative recovery was smooth.

PATHOLOGY. The macroscopic and radiographic appearances of the specimen were similar to those of the preceding two cases, but unfortunately the specimen was subsequently mislaid and no pathological studies were made.

PROGRESS. Since then her progress has been reasonably good, although she has functioned at a defective level. She has had no fits and no temper tantrums and her parents describe her behaviour as satisfactory. At the age of 5 years (Fig. 14) the Stanford-Binet Form L gave her mental age as $3\frac{1}{2}$ years and her I.Q. as 63. Since then she has made reasonable progress at school, and now, at the age of $8\frac{1}{2}$ years, can just read and write. Her left upper limb has remained very weak and is held flexed across her chest as before without any useful grip in the left hand. The left leg showed very little weakness, and the gait was only slightly abnormal. A number of tenotomy operations have been performed to correct a talipes equinus. Her present full scale intelligence quotient on the W.I.S.C. scale is 75 (D. Shalman), and she is attending a school for educationally subnormal children (Dr. A. C. Blandy).

Case 4. G.L., 16 years of age, was referred by Dr. N. Acheson. This youth, the eldest patient in our series, was born with a naevus covering most of the left face,

patchily over much of his body on the left side and to a slighter extent on the right side. A right hemiparesis was noted in early infancy. From the age of 4 months onwards he exhibited frequent epileptic attacks in which he rubbed his hands together, had slight twitches of his limbs, and was out of contact for one to two minutes. From the age of 14 years he had major convulsions lasting three to five minutes and recurring every four to six weeks in spite of medication. He had always been mentally defective and aggressive, and in recent years had exhibited frequent temper tantrums. His parents assessed his mental age as 4 to 5 years, and treated him as such. He wet his bed most nights.

EXAMINATION. He was small (5 ft. 2 in.) and underdeveloped. The naevus was extensive not only over the left face (Fig. 15), but over much of his body as well (Fig. 16). The left retina was a deeper red than the right and the left eyeball was bigger than the right. However, he appeared to see equally well with each eye, although a right homonymous hemianopia was present. A typical right-sided infantile hemiplegia was present with shortened spastic right limbs. His speech was limited to simple sentences, but he could neither count beyond 10 nor tell the time on a watch. He named common objects correctly. He stood in a stooped position and limped when he walked. His secondary sexual development seemed normal. An attempt was made to assess his intelligence quotient, but he proved untestable (Dr. V. Meyer).



FIG. 15.—Case 4, showing left facial naevus and left buphthalmos.

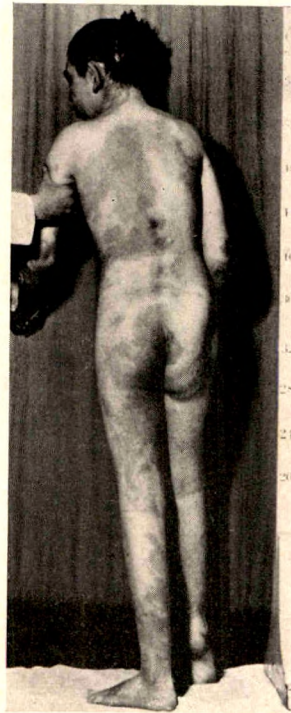


FIG. 16.—Case 4, showing patchy naevus over trunk.

INVESTIGATIONS. Skull radiographs showed a clear hemispherical atrophy with several large irregular blobs of calcification scattered throughout the left cerebral hemisphere (Fig. 17). Only in the occipital region could the double curvilinear lines which are more characteristic of Sturge-Weber disease be discerned. Pneumoencephalography disclosed a normal-sized ventricular system with, as in Case 1, considerable pooling of air in the subarachnoid spaces over the left cerebral cortex. The electroencephalogram showed almost complete absence of activity over the left hemisphere with normal alpha activity on the right side. No epileptic activity was seen in the routine records, but in a special study employing sphenoidal electrodes and thiopentone narcosis (Pampiglione and Kerridge, 1955) an active focus of spike discharges, both surface-negative and surface-positive was seen at the right sphenoidal area. We presumed, on clinical grounds, that this focus was being paced from the left side.

OPERATION. A left-sided craniotomy, performed on March 9, 1956, revealed an extensive angiomatic malformation of the Sylvian veins extending 6 cm. by 3 cm. (Fig. 18). The subarachnoid spaces over the rest of the hemisphere were covered with a close network of finer veins. Electrocorticography revealed a surprising amount of irregular slow-wave activity in the diseased hemisphere. The entire hemisphere except for its basal ganglia was then removed in one piece without much difficulty.

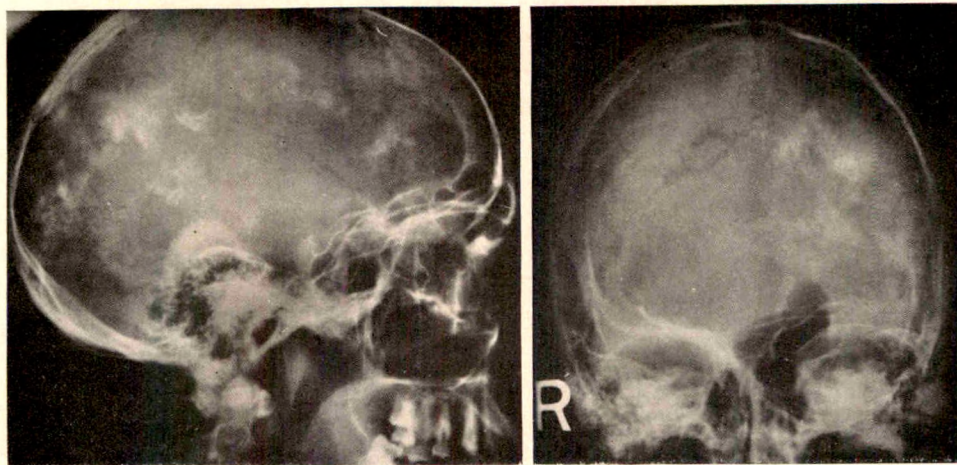


FIG. 17.—Case 4, radiographs showing peculiar type of cerebral calcification.

PATHOLOGY. Dr. Barbara Smith reported that two blocks of cortex showed 'a mass of dilated abnormal vessels embedded in connective tissue. In the outer layers of the cortex and in the white matter there were large masses of calcium, particularly in relation to the depths of the sulci. There was some gliosis of the cortex'. A diffuse angioma was present in the sub-arachnoid space (Fig. 19). A portion of the scalp with the naevus showed that the 'dermal papillae were more vascular than normal'. In the choroid plexus 'there was only a small area of normal choroid plexus. The rest consisted of an angioma with a number of calcified nodules'. A piece of the cranial vault showed 'no abnormality'.

PROGRESS. He made a good recovery from operation but there was no change in his neurological signs. His behaviour, however, was very much improved, and a month after operation it proved possible to assess his intelligence on the Wechsler-Bellvue scale (I.Q. 30).

Three years later his parents reported that he had had no fits since operation, and was 'more even-tempered and manageable'.

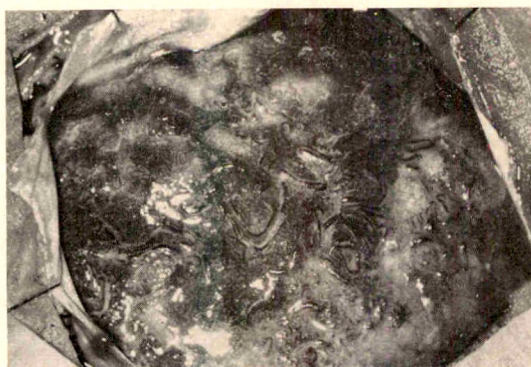


FIG. 18.—Case 4, operative appearances of left cerebral hemisphere as viewed from the head end of the operating table.



FIG. 19.—Case 4, photomicrograph showing a diffuse leptomeningeal angioma, extending into a sulcus. The cortex in the floor of the latter shows scattered masses of calcium. Haematoxylin and van Gieson $\times 7$.

Case 5. R.W., 12 years of age, was referred by Dr. I. MacKenzie. This boy was born with a naevus in the left forehead. At the age of 4½ months his mother noticed that he appeared disinclined to use the right hand. His progress between the ages of 4½ months and 2 years was slower than normal, and he did not walk until he was 2 years of age. At the age of 9 months he began to have convulsive seizures involving the right side of the body with loss of consciousness. These continued ranging in frequency from as many as 20 a day to as few as two or three a week. He started at an ordinary school when 5 years old, but at the age of 7 years was sent to a special school. There he did quite well and by the age of 8 years he could hold a conversation. At the age of 12 years he had only recently learnt to read and write, and to do simple arithmetic. There was no behavioural problem.

EXAMINATION. The typical telangiectasis involved the area of the ophthalmic division of the left trigeminal nerve, and the right side of the face was a little smaller than the left. His speech was normal. The optic fundi were normal, but a right homonymous hemianopia was present. There was a slight right lower facial weakness. The right limbs were slightly shorter than the left, and were also somewhat weak and spastic, but he could grip with his hand and had some individual finger movements. There was only slight weakness of the right leg, the muscle power being about 80% of normal. The tendon jerks were equal on the two sides, but the right plantar response was feebly extensor. Light touch and pain sensibility were normal on each side, but he had astereognosis in his right hand and two-point discrimination was unreliable. He walked well, but he was noticed to plant the right foot on the ground more firmly than the left. His intelligence rating on the Wechsler-Bellvue full scale was 57 (A. R. Dabbs).



FIG. 20.—Case 5, showing naevus.

INVESTIGATION. Skull radiographs showed that the left hemicranium was much smaller than the right, but the calcification indicative of Sturge-Weber disease was only present in a small area at the left occipital pole (Fig. 21). Pneumoencephalography, however, showed

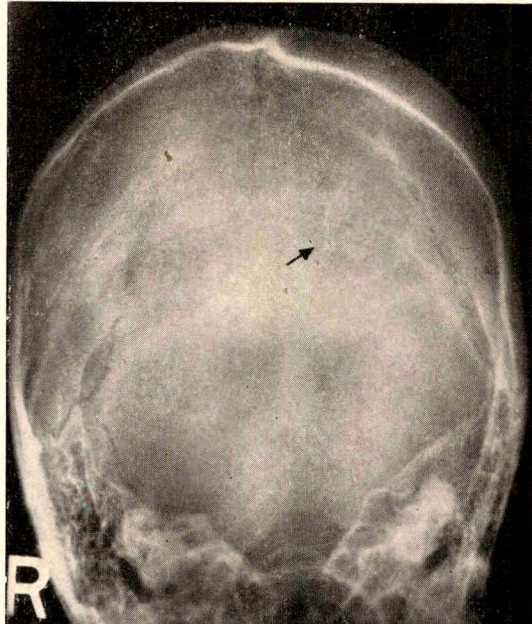


FIG. 21.—Case 5, radiographs (Towne's projection) showing characteristic calcification present at only a small area at left occipital pole (arrow).

that although the ventricular system was of normal size, the left cerebral hemisphere was shrunken with considerable pooling of air in its subarachnoid spaces (Fig. 22). Electroencephalography showed a 'gross reduction of both normal and barbiturate fast rhythm throughout the whole left hemisphere. A large amount of bilateral subcortical activity was seen better in the right side than the left. A few independent spikes were seen in the left frontal areas and occasionally on the right' (D. Hill).

OPERATION. A left-sided hemispherectomy was performed on July 17, 1956. The whole surface of the left cerebral hemisphere was seen to be covered by an angiomatous malformation similar to our previous cases. Electrocorticography revealed poor activity over the posterior two-thirds of the hemisphere with relatively normal activity in the frontal region, where occasional spike discharges were seen (G. Pampiglione).

PATHOLOGY. Although the surface of the cerebral hemisphere presented an evenly distributed flushed appearance of the cortex and leptomeninges (Fig. 23), radiographs of the specimen disclosed calcification only



FIG. 22.—Case 5, antero-posterior air encephalogram showing shrunken left cerebral hemisphere with capacious subarachnoid spaces.

at the occipital pole (Fig. 24). Dr. Barbara Smith reported on a block from the parietal lobe as follows:

'The thickened pia-arachnoid was full of large vascular spaces with thin collagenous walls. These spaces did not involve the nervous tissue itself. There were an increased number of astrocytes in the cortex, particularly in the superficial layers, and considerable submarginal gliosis. Some of the neurones showed ferruginous incrustation. There was only a small amount of calcium in the cortex.'

PROGRESS. The postoperative course has been smooth, and he has not subsequently had any further fits during the three year follow-up period. At first,



FIG. 23.—Case 5, view of resected hemisphere showing diffuse vascularity of the pia-arachnoid.

however, his right hemiparesis was markedly increased, and during the first two weeks there was very little voluntary movement in either the right arm or the right leg. Also there was some questionable dysphasia, while sensibility to touch and pinprick was impaired on the right side. Thereafter, however, there was a gradual improvement in power and sensation, so that six weeks after operation, when he was discharged, he could walk again. At that time he had some voluntary movement of the shoulder and elbow, but none of the wrist and fingers. Power at the right hip and knee was approximately 30% of normal, but there was a foot drop. Sensibility had returned to its preoperative level. Psychological testing now gave an I.Q. of 70 on the Wechsler scale, but it was thought that this apparent improvement was not statistically significant and



FIG. 24.—Case 5, radiograph of specimen showing characteristic calcification only at occipital pole.

might be the result of practice. The E.E.G. was flat on the left, and showed normal alpha rhythm on the right side. A short burst of wave and spike activity was seen on over-breathing (D. Hill). The most recent intelligence quotient on the W.I.S.C. scale is 66 (D. Shalman). The patient had commenced work as a messenger boy.

Discussion

These five cases are all well marked examples of Sturge-Weber disease, the essential abnormality of which is the congenital lepto-meningeal venous angioma. Our cases conform to the excellent recent descriptions of pathological data given by Medoc *et al.* (1953-54), by Lichtenstein (1954), by Wohlwill and Yakovlev (1957), and by Norman (1958). The angioma brings about a progressive destruction of the cerebral cortex, and the clinical effects depend upon the location of the damage and the rapidity with which it occurs. It does not lead to an intracranial bruit.

The case histories of our patients are typical of the more advanced cases of this condition and the

TABLE
SUMMARY OF RESULTS OF OPERATION

Case No.	Clinical Features at Time of Operation					Clinical Features at Time of Follow-up			
	Age (yrs)	Sex	Laterality of Affected Hemisphere	Epilepsy	Behaviour	Duration of Follow-up (yrs)	Epilepsy	Behaviour	Intelligence
1	3½	M	Left	Several attacks daily	Sullen	8	Fit-free	Sociable	Improved, educable
2	6	F	Left	Two to three attacks per week	Frequent temper tantrums	7½	Fit-free	Sociable	Improved, educable
3	3½	F	Right	Fits had ceased during infancy	Frequent temper tantrums	5	Fit-free	Sociable	Improved, educable
4	16	M	Left	Fits every month	Frequent temper tantrums	3	Fit-free	Satisfactory	Still grossly defective
5	12	M	Left	Several attacks daily	Normal	3	Fit-free	Still normal	Improved, educable

salient features are summarized in the Table. At birth the infant appears quite normal apart from the unilateral facial telangiectasis. After a varying period, in our cases from 3 weeks to 9 months, the child begins to have epileptic seizures which initially involve the side of the body contralateral to the naevus. Later they may spread to the other side as well. The frequency and severity of the fits vary widely. At about the same time as the fits commence, the limbs in the side opposite to the naevus are noted to be weak. This weakness apparently increases as the child grows, and may develop into a marked infantile hemiplegia with wasted shortened and spastic limbs. Further, as the child grows older, mental backwardness becomes evident, and temper tantrums and other behaviour disorders may make their appearance. The characteristic calcification seen in radiographs may be absent in early infancy, and not appear until later. The combination of epilepsy, backwardness and unmanageability may make institutional care necessary. All five of our cases had both facial naevus and infantile hemiplegia. Cases 1, 2 and 4 exhibited the most complete clinical pictures; Case 3 had only a transient epilepsy, but a persistent personality disorder, and Case 5 had epilepsy but a normal personality.

Our cases also illustrate well the value of radiology in this condition, a topic which has recently been intensively reported by Poser and Taveras (1957). All five cases showed marked hemispherical atrophy with a shrunken cerebral hemisphere, which was well outlined in four of the cases by the characteristic calcification and in all five cases by pneumoencephalography. In two cases (Case 1 and 2) calcification was not noted in the skull radiographs taken in infancy, but was markedly developed by

the third year of life. Poser and Taveras (1957) also remark on this. In Case 5 the calcification was detectable only in the occipital pole even although the angioma was widespread. Carotid angiography was performed in only two of our cases, both during infancy, and no vascular abnormality was noted. Such a negative finding (except for evidence of hemispherical atrophy) agrees with the usual consensus of opinion (Moniz and Lima, 1935; Bergstrand, Olivecrona and Tönnis, 1936; Riechert, 1943). However, Poser and Taveras (1957) point out that in many cases the presence of the capillary-venous angioma can be disclosed by serial angiography, and that other lesions such as arterial thromboses and external carotid artery anomalies may be disclosed. Only one case with a cirroid arterio-venous malformation appears to have been reported. None of our cases had suffered from intracranial haemorrhage, although instances both of subarachnoid haemorrhage and of subdural haemorrhage have been reported in this condition (Cushing, 1906; Poser and Taveras, 1957).

There are still comparatively few case reports in the literature of operative intervention for Sturge-Weber disease. Balado (Dimitri and Balado, 1933) performed a craniotomy under local anaesthesia in 1930 on Dr. Dimitri's patient, then aged about 20 years, exposing a cirroid venous angioma which he treated by electrocoagulation of the principal surface vessels without any alteration in consciousness. Subsequently the patient continued to have attacks, but with a reduced frequency. Krayenbühl *et al.* (1957) state that Tönnis, in 1934, tried the same procedure, but did not describe the results.

A few neurosurgeons report cases in which the Sturge-Weber malformations appear to have been localized to a small part of the cerebral hemisphere

which was then excised, apparently with benefit. Thus Broager and Hertz (1949) report the case of a 5-year-old boy in which the left premotor region was excised largely on E.E.G. evidence. There was a naevus of the face and a naevus on the inner side of the dura in the premotor region, while a number of fine tortuous vessels were noted in the pia of the affected region. The patient was followed up for one year, and was free of fits, but still on anticonvulsive medication. Other surgeons who have reported comparable cases include Green, Foster and Berens (1950), occipital lobe with characteristic calcification; Huber and Zweymüller (1954), parietal lobe; and Krayenbühl *et al.* (1957), temporal lobe. However, a recurrence of epilepsy can follow upon these limited excisions (Krayenbühl, 1959).

Cairns and Davidson (1951) record the first case successfully treated by hemispherectomy. This was a 7-year-old girl with infantile hemiplegia, fits and behavioural disturbances. One year later she was free of fits, her intelligence quotient had risen from 63 to 73, and she appeared educable. Polani (1952) in the following year, gave a preliminary report on the first two cases included in this present paper. Obrador Alcalde (1958), in a recent paper, mentions that other cases have been successfully operated on by Paillas and by McKissock (Laine and Gros, 1956), by French *et al.* (1955), and by Goodall (1957), and he adds a sixth case report from his own experience. This was an 11-year-old patient observed to be free from fits 14 months after the operation.

A recent report from the Mayo Clinic (Peterman *et al.*, 1958) mentions that operation was carried out in four of 35 cases seen in the period from 1935 to 1956. Three of these cases had been submitted to a lobectomy rather than to a hemispherectomy with relief of seizures in one case. The fourth patient had undergone a craniotomy, but the lesion was not extirpated because of the extent of the angioma. Of the 35 cases, 31 had had adequate follow-up studies, and these showed the variability which is encountered in the course of this disease; 17 of the patients were considered well, and two had never had a convulsion; 15 had continued to have seizures, some, however, infrequently. One other of their patients had undergone a cortical excision elsewhere with a successful result. Four patients had died, one after craniotomy and three after progressive deterioration at ages between 9 months and 7½ years. Ten patients had done poorly, five being confined to institutions. Of the 17 patients who had done well, only three showed mental retardation. One indeed had graduated

from college, and several were married and rearing families.

The drastic procedure of cerebral hemispherectomy or the less severe one of lobectomy are therefore justified only when there is a proper indication, i.e. disabling epilepsy and/or a personality disorder. If the angiomatous lesion is circumscribed in the brain, a local extirpation may be all that is necessary (Broager and Hertz, 1949), but, if it is widespread throughout one cerebral hemisphere, removal of that hemisphere is indicated.

Our cases show that provided the other hemisphere is structurally normal, hemispherectomy may be confidently expected to abolish the seizures and produce a real improvement in the personality. The infantile hemiplegia is not improved, and subsequent operative procedures may prove necessary to correct a talipes equinus. The patient remains backward, but his intelligence as rated by the usual tests may improve a little even in relation to his increased age, and he may function as a high-grade mental defective and be educable. Thus it has led to improvement in learning in all four of our patients who were operated upon during childhood. It did not benefit Case 4 who was operated upon as an adult. Our experience in all these respects is in agreement with the results of hemispherectomy performed for other types of infantile hemiplegia (Krynauw, 1950).

Before the operation is undertaken, the condition of the other hemisphere is checked by pneumoencephalography and electroencephalography. Pooling of air over the surface in dilated subarachnoid spaces or ventricular dilatation on the supposedly good side indicates damage to it. The electroencephalographic findings need to be interpreted with caution. Krynauw (1950) demonstrated in his cases of infantile hemiplegia that E.E.G. abnormalities in the good hemisphere often cleared up after removal of the diseased one. This may explain both the postoperative improvement in personality and in intelligence.

Given proper indications, the operation is well worthwhile, and the question arises as to the best stage at which it should be performed. An opinion in this respect is largely based on theoretical premises. We have no evidence to suppose that it will benefit a child with infantile hemiplegia but without epilepsy or a personality disorder. If, however, one or both of these is present (and in our cases they had all appeared within the first year of life), the child should be operated on at an early stage in order to stop the seizures and improve learning capacity. The skull of a young infant, however, because of its flexibility, makes the closure

of a large craniotomy difficult. The youngest age at which operation was performed in this series was 3½ years, and no great difficulty was encountered. On theoretical grounds the child could have been operated on with equal ease between the ages of 2 and 3 years, which is probably the preferable age period. As in other conditions causing infantile hemiplegia, aphasia does not appear, even when the left cerebral hemisphere is removed (Krynauw, 1950).

Summary

The case histories of five patients with advanced Sturge-Weber disease (encephalotrigeminal angiomas) are recorded. All exhibited epilepsy and/or a behavioural disturbance occurring in association with an infantile hemiplegia and their epilepsy and personality conditions were improved by excision of the affected cerebral hemisphere (hemispherectomy), but not their infantile hemiplegia. All remained mentally backward, but the four who were operated on during childhood proved to be educable. These findings conform to the observations made by others who have performed hemispherectomy for this condition.

We wish to thank the various physicians who have referred us their cases. In particular we are grateful to Dr. P. R. Evans, Mr. P. H. Schurr, Professor P. M. Daniel, Dr. A. L. Woolf, and Dr. Barbara Smith who have helped us with the text, and the various psychologists who have given us their reports. The radiographs were provided by Dr. E. D. Hoare. We are also grateful to the Medical Research Council for a grant towards the investigation of patients with epilepsy treated by surgery which has made the follow-up possible.

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COMPARISON OF CHANGES IN SERUM PROTEINS DURING EARLY TREATMENT IN KWASHIORKOR AND MARASMUS

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Kwashiorkor and marasmus are the two commonest forms of infant malnutrition found in tropical countries and the fundamental aetiological difference between them appears to be in the proportion of carbohydrate in the diet. The diet leading to marasmus seems to be reasonably balanced though insufficient in quantity and therefore in calories as well as protein, whereas the diet leading to kwashiorkor is imbalanced in that there is a protein deficiency but a relative excess of carbohydrates which can lead to an adequate calorie intake. The clinical picture in these two types of malnutrition is strikingly different. Though protein deficiency in the aetiology of kwashiorkor has been emphasized, and without doubt is present in these infants, perhaps insufficient attention has been paid to the carbohydrate metabolism in kwashiorkor. Before going so far as to suggest that the clinical signs of kwashiorkor are related to a relative excess of carbohydrate, and that it is this excess which gives rise to the oedema, skin and hair changes and fatty liver, either directly or indirectly, seen in kwashiorkor and not in marasmus, it was thought that a comparison of the protein metabolism in the two states might show whether in fact protein metabolism differed in the two conditions. If a difference is present, then one can, with more justification, designate kwashiorkor as protein malnutrition; if there is no difference, apart from that of degree, then it is possible that kwashiorkor is no more nor less dependent on protein malnutrition than is marasmus and the emphasis in aetiology should perhaps be shifted to carbohydrate.

A simple approach to this problem lies in the study of the serum proteins, and especially in the first few days of treatment when the body is faced

with the possibility of repairing the damage in the protein metabolism. It can be assumed that those parts of the protein 'workshop' most severely disorganized by the previous state of protein shortage, and possibly imbalance, would respond to treatment at a rate different from that of the less severely affected mechanisms and this might be reflected in the serum protein levels in the early days of treatment.

Methods

There are many cases which show some signs of kwashiorkor and of marasmus, the so-called marasmic kwashiorkor, but in this study cases were deliberately chosen which were as near the extremes as possible so that the kwashiorkor group all had hair and skin changes and gross oedema, whilst the marasmic group had none of these signs. The mental state, the apathy of the kwashiorkor, was present in all the cases studied, whereas in the marasmic group all the children on admission had a noticeable mental alertness, being very interested and apprehensive of their surroundings. Though liver biopsy was not done, the cases were clinically distinct and of one type of malnutrition or the other.

The children were all aged 1 to 4 years inclusive.

Approximately 2 ml. of blood were taken before treatment commenced and on each subsequent morning until the 14th day in hospital. The blood was allowed to clot and the serum decanted off. After centrifugation the total serum proteins were estimated by refractometry and then subjected to paper electrophoresis. The proportion of protein present was assessed by measuring the density of the various protein bands.

The treatment given to the patients was not controlled in any way, it being left to the clinician in charge to give drugs, etc., according to clinical needs. However, the composition of the diet for kwashiorkor was standard and consisted mainly of whole powdered milk, with casein and sugar until the sixth day, after which vegetables, meat, fish, etc., were added. The diet of the marasmic cases was qualitatively the same as the kwashiorkor.

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Results

Kwashiorkor. The various protein fractions in the serum as determined daily are expressed both as g. % and as percentages of the total serum proteins. The results are seen in Table 1 and Figs. 1 and 2 and represent the means of seven cases.

The pre-treatment values reported here were lower for albumin and the increase in the albumin in response to treatment was not so striking as reported by Davin (1955). This slower rise is presumably because protein hydrolysate is not now

added to the diet as it was when Davin carried out his studies in the same hospital.

The alterations seen in the percentage of the various fractions in kwashiorkor at the commencement of treatment are not all to the same degree when compared with the mean values of a series of 41 normal African children (Table 2). In contrast to the albumin fraction which is lower, the α_1 and γ globulin percentages are higher, whilst the α_2 and β remain approximately the same. The drop in total proteins, however, is such that all fractions

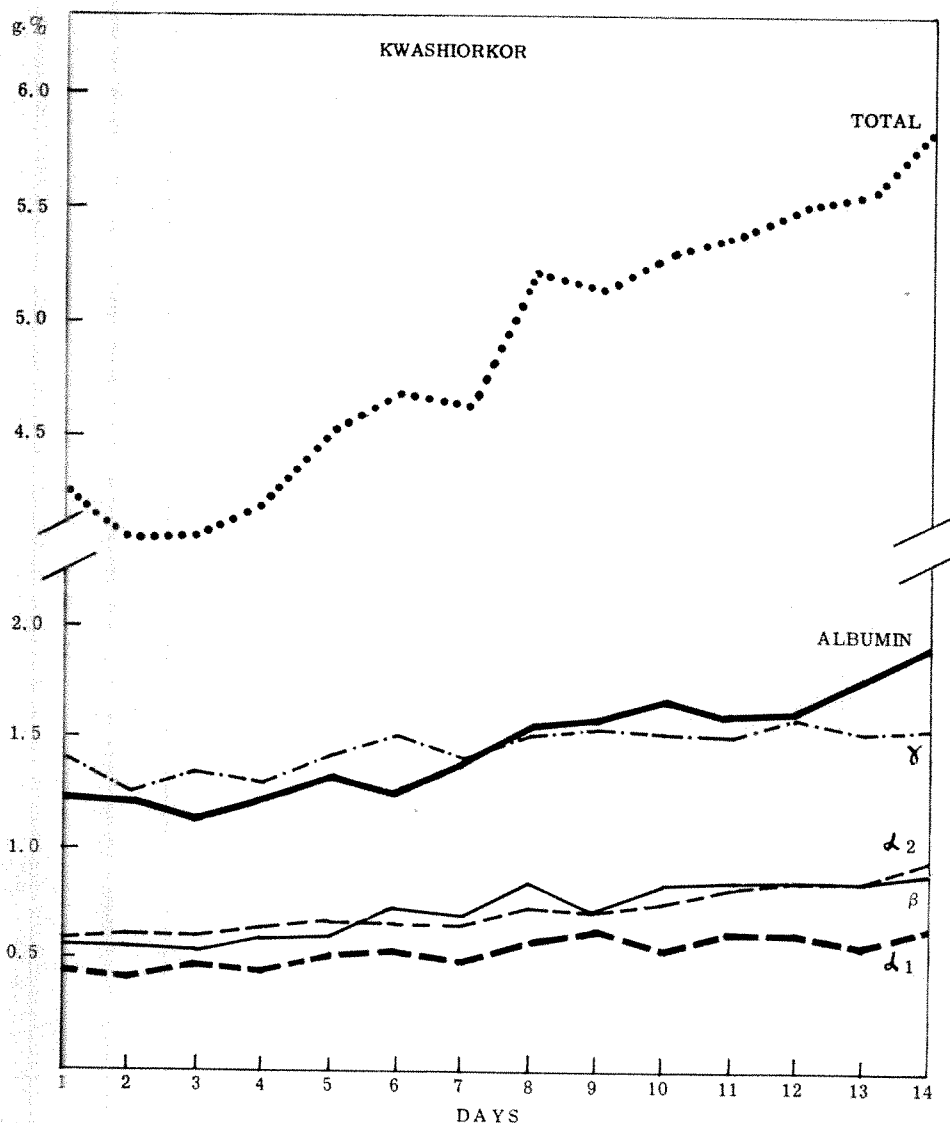


FIG. 1.—Mean g. % values for serum protein fractions during early treatment in kwashiorkor.

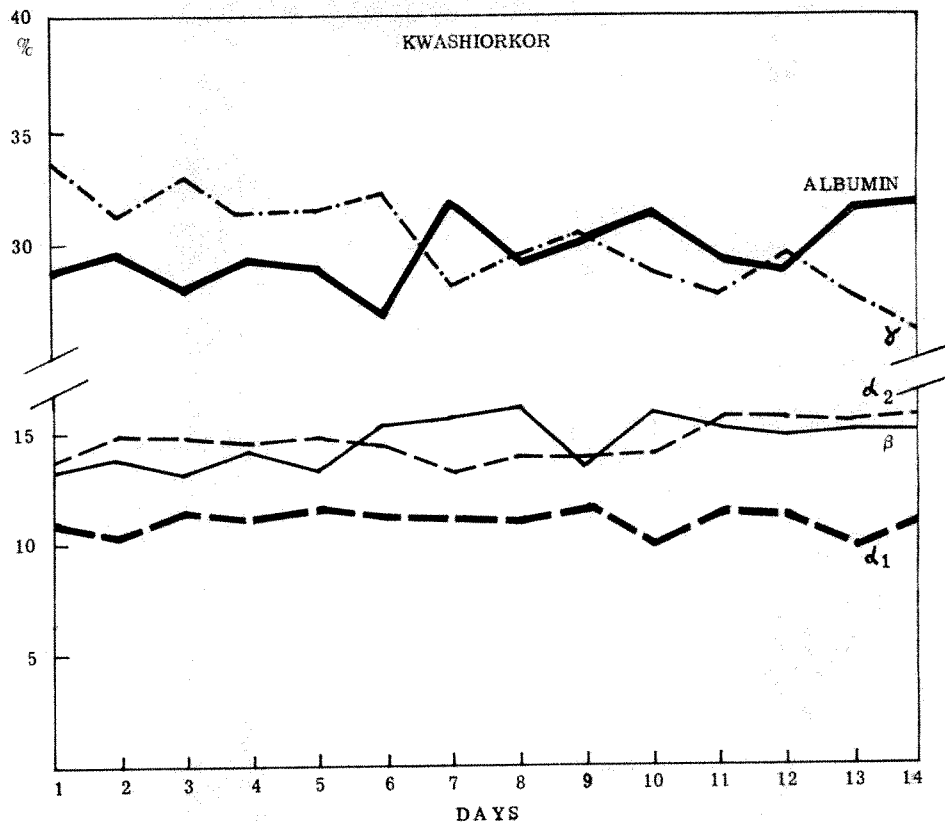


FIG. 2.—Mean % values for serum protein fractions during early treatment in kwashiorkor.

when expressed as g. % are lower in value, though less obviously so in α_1 and β globulins.

The total proteins increase during treatment at a fairly constant rate except for a slight reduction in the first two days of treatment. This may be

due to increased blood volume consequent upon the removal of oedema fluid, and rehydration therapy.

It can be seen that the proportion of albumin tends to rise ($p = 0.05$), whilst the α_1 globulin is

TABLE I
MEAN DAILY VALUES OF SERUM PROTEINS IN CASES OF KWASHIORKOR

Day	Total Protein (g. %)	Albumin (g. %)	α_1 g. %	α_2 g. %	β g. %	γ g. %	Albumin (%)	α_1 %	α_2 %	β %	γ %
1	4.26	1.23	0.46	0.59	0.56	1.42	28.8	10.8	13.7	13.2	33.5
2	4.04	1.21	0.42	0.60	0.56	1.25	29.5	10.3	14.8	13.9	31.4
3	4.06	1.12	0.47	0.60	0.53	1.34	27.9	11.4	14.7	13.1	32.9
4	4.19	1.22	0.46	0.61	0.60	1.30	29.3	11.1	14.4	14.1	31.1
5	4.51	1.31	0.52	0.67	0.60	1.41	28.8	11.6	14.8	13.3	31.4
6	4.70	1.26	0.53	0.67	0.73	1.51	26.8	11.2	14.4	15.4	32.1
7	4.64	1.38	0.49	0.67	0.69	1.41	31.9	11.2	13.2	15.6	28.0
8	5.24	1.59	0.58	0.74	0.86	1.53	29.2	11.1	14.0	16.2	29.4
9	5.17	1.59	0.61	0.71	0.71	1.55	30.1	11.8	13.9	13.5	30.6
10	5.33	1.67	0.53	0.76	0.84	1.53	31.4	10.0	14.1	15.7	28.8
11	5.33	1.39	0.62	0.84	0.85	1.50	29.3	11.5	15.7	15.5	27.9
12	5.40	1.62	0.61	0.86	0.85	1.60	28.7	11.2	15.7	15.0	29.4
13	5.54	1.79	0.55	0.86	0.87	1.53	31.5	9.9	15.6	15.3	27.7
14	5.60	1.91	0.64	0.94	0.90	1.54	31.8	11.0	15.9	15.1	26.2
P	0.001	0.001	0.001	0.001	0.001	0.001	0.05	0.05	-0.05	0.025	0.001
Normal Values	7.37	3.28	0.57	0.97	0.92	1.62	44.5	7.8	13.2	12.5	22.0

TABLE 2

MEAN % OF VARIOUS SERUM PROTEIN FRACTIONS IN SEVEN CASES OF KWASHIORKOR AND SEVEN CASES OF MARASMUS AND IN A NORMAL SERIES (DAVIN, 1955)

	Albumin	Globulin			
		α_1	α_2	β	γ
Kwashiorkor	28.8	10.8	13.7	13.2	33.5
Marasmus	36.0	10.8	12.8	11.5	28.9
Normal	44.5	7.8	13.2	12.5	22.0

TABLE 3

CHANGE COMPARED WITH NORMAL IN VARIOUS FRACTIONS OF SERUM PROTEINS AT COMMENCEMENT OF TREATMENT EXPRESSED AS % RISE OR FALL FROM NORMAL

	Kwashiorkor	Marasmus
Albumin	-62	-39
α_1	-19	+5
α_2	-39	-30
β	-39	-32
γ	-12	-4

constant. The α_2 globulin rises ($p = 0.05-0.025$) as does the β globulin ($p = 0.025-0.01$), whereas the γ fraction falls ($p = 0.001$) in the first 14 days of treatment. These changes are reflected in the results expressed as g. % except for the γ globulins where a rise is now seen, and in the α_1 fraction where the constant percentage means that with an increasing total serum protein the g. % of this fraction shows a rise.

Davin (1955) carried out serum electrophoresis before treatment and after seven to 12 days of treatment in cases of kwashiorkor and his results showed the same proportional tendencies with treatment as those reported here, though there are slight differences in the actual values in the two groups.

These results compare favourably with those of Autret and Behar (1954) but as these authors do not separate the α globulins in their control sera it cannot be seen if they also found a rise in α_1 globulin.

The relative fall in the level of each serum protein component in kwashiorkor, compared to normal, is not constant. In the present seven cases the mean albumin level was 62% lower, and the α_2 and β 39%, α_1 19% and γ 12% lower than Davin's normal figures (Table 3) (Davin, 1955). The reason for

this is not known, but it must reflect different metabolic activities in the various serum proteins, though whether these are based on supply or demand cannot appear from this study.

Marasmus. The results of the serum protein changes in the first 14 days of treatment in marasmic infants are seen in Table 4 and Figs. 3 and 4. There are some differences when compared to the kwashiorkor group at the commencement of treatment, mainly in the total serum protein level which is not so low in the marasmics, largely as a result of the higher albumin level in these cases.

As with kwashiorkor, the changes in the relative levels of the serum protein components are not constant (Table 3). The albumin level was 39% below normal, the α_2 and β fell approximately 35% and the α_1 and γ showed little change.

Hence in these two conditions of infant malnutrition the α_2 and β seem to be linked and equally affected, whereas the reduction in albumin, similar to that in α_2 and β in marasmus, is much more marked in kwashiorkor, the least proportional changes being seen in the α_1 and γ globulins.

If the rate of increase in the g. % of each of the serum proteins in the kwashiorkor and marasmus groups is compared it is found that all the serum

TABLE 4
THE MEAN DAILY VALUES OF SERUM PROTEINS IN THE CASES OF MARASMUS

Day	Total Protein (g. %)	Albumin (g. %)	α_1 g. %	α_2 g. %	β g. %	γ g. %	Albumin (%)	α_1 %	α_2 %	β %	γ %
1	5.45	1.99	0.60	0.68	0.63	1.55	36.0	10.8	12.8	11.5	28.9
2	5.29	1.89	0.49	0.73	0.64	1.54	35.5	9.3	13.9	11.8	29.5
3	5.39	1.84	0.48	0.74	0.64	1.60	34.7	9.3	13.9	11.8	30.3
4	5.45	2.00	0.48	0.73	0.64	1.60	36.7	9.0	13.3	11.5	29.5
5	5.50	2.00	0.54	0.73	0.63	1.60	36.3	9.9	13.2	11.4	29.3
6	5.49	1.97	0.48	0.74	0.64	1.66	36.1	8.8	13.4	11.4	30.2
7	5.65	2.12	0.48	0.76	0.70	1.60	36.0	8.7	13.9	12.3	29.1
8	5.63	2.11	0.48	0.73	0.70	1.66	37.3	8.5	12.8	11.9	29.4
9	5.79	2.19	0.49	0.71	0.71	1.69	37.7	8.5	12.4	12.1	29.2
10	5.79	2.18	0.47	0.74	0.73	1.67	37.7	8.2	12.8	12.5	28.8
11	6.05	2.28	0.54	0.83	0.71	1.69	37.5	9.0	13.7	11.6	28.1
12	6.13	2.39	0.55	0.78	0.76	1.65	38.5	9.2	13.0	12.3	27.0
13	6.10	2.40	0.52	0.79	0.74	1.65	38.9	8.7	13.0	12.1	27.3
14	6.39	2.38	0.51	0.86	0.85	1.79	37.1	8.1	13.7	13.1	28.1
P	0.001	0.001	0.1	0.005	0.001	0.001	0.005	0.01	0.5	0.01	0.005
				-0.001				-0.005		-0.005	-0.001

proteins increase at a greater rate in kwashiorkor than in marasmus except for the γ globulins, whose rate of change is the same.

Discussion

The similar serum protein pattern found in kwashiorkor and marasmus suggests that the protein metabolism in both types of malnutrition differs only in degree, and that marasmus is as much a protein malnutrition as is kwashiorkor. Its more rapid response to treatment supports the view that

kwashiorkor is a more acute form of malnutrition than marasmus, though it is difficult to comprehend how rate of onset can influence rate of response to treatment.

In both kwashiorkor and marasmus there is a deficiency of adequate protein intake and the pattern of the serum proteins is the same in each except that the reduction in serum albumin is greater in kwashiorkor. The apparent link, in the extent of the change from normal between α_1 and γ globulins and between α_2 and β globulins in both con-

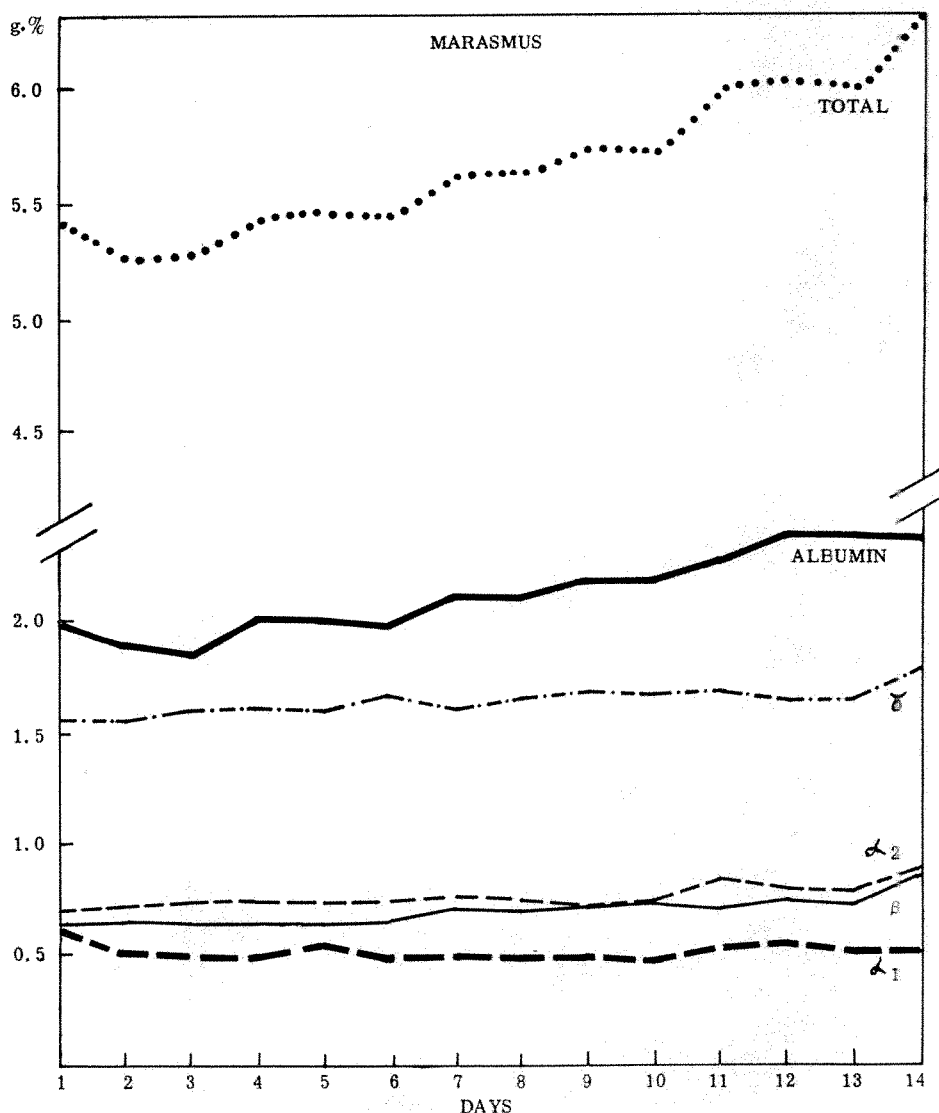


FIG. 3.—Mean g. % values for serum protein fractions during early treatment in marasmus.

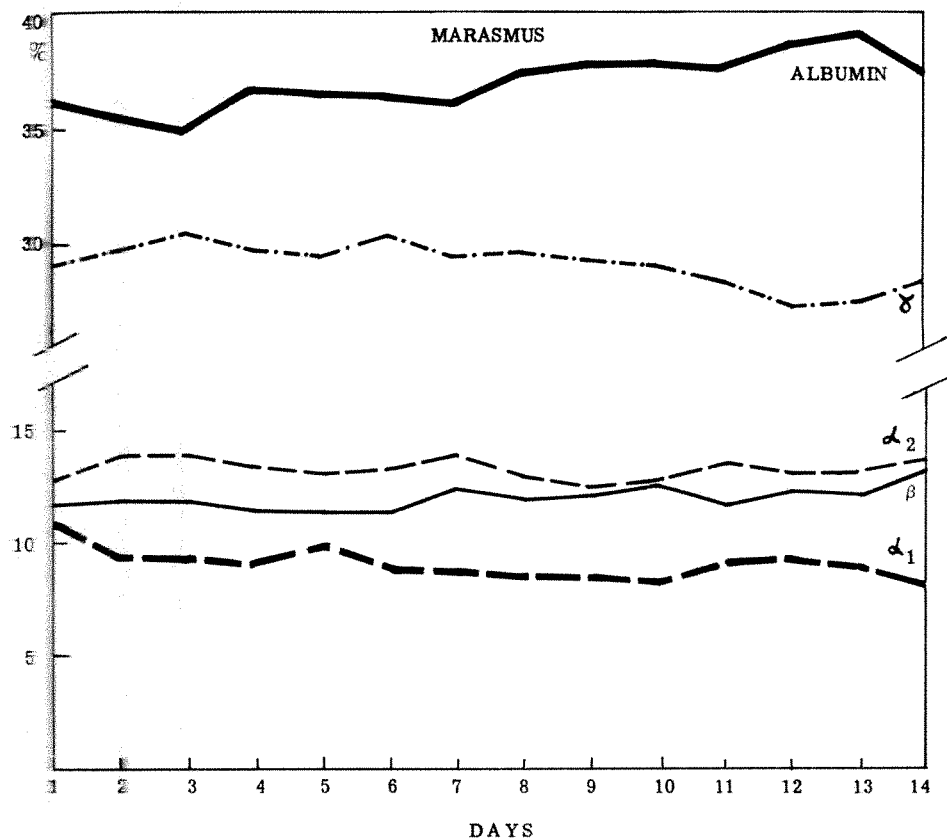


FIG. 4.—Mean % values for serum protein fractions during early treatment in marasmus.

ditions, suggests a common error in protein metabolism because these proteins are not equally affected in this way in other diseased states. If one assumes that the protein metabolism in the two conditions is affected in a similar way, and that there is no reason why protein metabolism should be different in these two types of infant malnutrition which have in common a deficient intake of adequate protein, then the clinical differences must be due to some factor other than protein.

The main difference in the diet leading to these two types of malnutrition is a relative excess of carbohydrate in the pre-kwashiorkor intake. As it is suggested that protein metabolism is similar in these two kinds of malnutrition, then it is possible that the clinical picture of kwashiorkor is due, not solely to protein malnutrition but to a relative excess of dietary carbohydrate (Macdonald, 1960).

The rate of protein recovery is more rapid in kwashiorkor. The γ globulin shows little fall in either condition and the response to treatment is

similar, and it is possible that the γ globulin has not to any extent been influenced by the inadequate protein intake but only by the infection contracted by the child.

An interesting feature in these results is the apparently close relationship between α_1 and γ globulin and between α_2 and β globulin. The extent of the fall in each pair as well as the rate of response to treatment is similar. This suggests that the metabolic processes concerned in the production and utilization of these two pairs of serum proteins are closely allied.

These results therefore show that before the commencement of treatment the pattern of change in the serum proteins in kwashiorkor and marasmus is similar. The serum protein response to an identical diet is also similar in the two conditions, the differences being in degree only. Thus no evidence can be found in this study to suggest that protein metabolism is qualitatively different in kwashiorkor from that in marasmus.

Summary

Daily serum protein electrophoresis for the first 13 days of treatment in seven cases of kwashiorkor and seven cases of marasmus reveals no difference qualitatively in serum protein response to a diet which was similar in all cases.

It is suggested that the protein metabolism in kwashiorkor is similar to that in marasmus, and that the clinical differences found between the two conditions are due to some other factor, possibly the relative excess of dietary carbohydrate.

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HIGH PROTEIN FEEDING IN KWASHIORKOR*

BY

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The highly satisfactory results with skimmed cow's milk in the treatment of uncomplicated kwashiorkor are well documented. Dean (1953) stated that a patient needed 50 g. protein daily, but in 1956 recommended that fat be added as well. It has been suggested that very high protein intake, by supplementing cow's milk with concentrated powdered milk protein, may hasten the cure of the disease. Many hospitals still use this expensive therapy. Pretorius, Hansen, Davel and Brock (1956), however, did not observe benefit from supplementing skimmed milk, and it has also been suggested that too high a protein diet may cause harm and even sudden death (Gyorgy, 1955; S  n  cal, 1958).

It was therefore decided to study this problem as part of an investigation, initiated in November, 1957, into anaemia in kwashiorkor (Walt, 1959). Alternate cases were given a protein supplement and a comparison of the total daily protein and caloric intake, daily weight change and weekly serum protein estimations in cases in each group was undertaken.

Material and Methods

Six hospital beds were made available for the study and as each bed became vacant, a new patient with kwashiorkor was admitted to the trial. All the patients were ill, necessitating admission to hospital. Many had superimposed infections.

A full clinical examination was carried out on every patient by the first author, and, without his prior knowledge, allotted alternately to the two treatment groups.

From November 22, 1957, to June 29, 1958, 45 patients were admitted to the trial. Five patients in each treatment group died, leaving 35 cases for analysis. These cases were observed for 28 days.

Treatment Groups. Skimmed lactic acid milk only (SLAM) was administered in 17 cases; skimmed lactic acid milk plus protein supplement (SLAM + PS) was administered in 18 cases.

From July 15, 1958, to June 22, 1959, a further 48 cases, comprising the second series, were admitted. There were 12 deaths; two cases were excluded because of tuberculosis and two cases because of unreliable records. This left 32 cases for analysis. These cases were observed for 42 days: skimmed lactic acid milk, plus injectable iron (SLAM + Fe) was administered from the eighth hospital day to 13 cases; skimmed lactic acid milk plus protein supplement (SLAM + PS) ('Tervamix'), as in the first series to 19 cases.

It will be noted that the only difference between the first and second series of cases was the addition of iron injections after the eighth day to the non-supplemented group. Table 1 shows that the severity of kwashiorkor was similar in both groups, as was the number of patients requiring intravenous therapy and/or blood transfusions. There was a similar proportion of infections in the two groups. The average age for the SLAM + PS group was 18 months and for the other 20 months. All the patients were of African (Bantu) origin. An analysis of the deaths among the total of 93 cases admitted showed that the median days of death in the SLAM group and SLAM + PS groups were the fourth and third days respectively. Statistically there was no significant difference in the death rates of the two groups.

TABLE 1

Cases	Treatment	
	SLAM	SLAM + PS
Cases admitted	46	47
Deaths	14	8
Cases excluded	2	2
Cases analysed	30	37
Mean age (months)	20	18
Severity of illness on admission:		
Mild	9 (30%)	12 (32%)
Moderate	16 (53%)	19 (52%)
Severe	5 (17%)	6 (16%)
Cases requiring intravenous therapy	6	9
Blood transfusions	3	3
Cases with infections:		
In first week	10 (33%)	16 (43%)
During hospitalization	21 (70%)	26 (70%)

Feeding. Lactified skimmed cow's milk (Walt, Wills and Nightingale, 1950) was offered to all patients. They were encouraged and coaxed to drink as much as they wished by the nursing staff, who are taught to be

* Presented at the 1st Congress of the Nutrition Society of Southern Africa on November 16, 1959, at Pretoria.

kindly and patient with these difficult children. The minimum quantities offered for the first three days were $1\frac{1}{2}$, 2 and $2\frac{1}{2}$ oz. per lb. body weight respectively. Full ward diet was introduced on the 15th day.

The alternate patients received a supplement of 'Tervamix', a powder containing 68% milk protein (casein), obtained from skimmed milk. It was added to the lactified milk in the proportion of $1\frac{1}{2}$ g. per lb. body weight, thus providing an extra 1 g. protein per lb. body weight per day.

Additional Routine Therapy on Admission. The following was administered to all patients: procaine penicillin 300,000 units intramuscularly daily for seven days; triple sulphonamide 90 mg. per lb. body weight daily for seven days; vitamin C, 50 mg. daily; potassium chloride, 5 gr. three times per day for seven days; folic acid ('Folvite') 7.5 mg. intramuscularly daily for three days, followed by 5 mg. orally three times per day for 25 days; intramuscular iron ('Imferon'), on the recommended basis, was given from the eighth day to the patients in the second series not receiving protein supplement (SLAM + Fe).

Measurements. All patients were weighed by the paediatric registrar daily just before the 9 a.m. feed, at the same time as the protein supplement was weighed. The daily quantity of feed taken by each patient was accurately measured and recorded allowing the daily protein and caloric intake to be estimated (Fig. 1).

Serum Proteins. Serum protein estimation and electrophoresis were performed on admission and weekly thereafter by the methods of Joubert, Hookins and Hunter (1959).

Results

The addition of injectable iron to the patients in the non-supplemented group in the second series apparently did not affect the protein and caloric intakes, weight changes and serum protein levels materially. Therefore, for purposes of analysis, the results of the non-supplemented groups in the first and second series of cases have been combined and compared with the results of the protein-supplemented cases from both series. Figs. 1, 2 and 3, and Table 2 summarize some of the findings in the two groups.

Response to Treatment. All 67 cases recovered well and were discharged from hospital at the end of the period of observation; many could have been discharged earlier. The patients had their diuresis between the fourth and 12th days; clinical oedema tended to disappear earlier in the protein-supplemented group. By the end of 14 days, the skin lesions were healed and the patients smiling, a sign of recovery which we find very useful; their appetites were good and dispositions happy unless some infection supervened. These infections were a constant source of worry, and in the majority of cases necessitated the use of appropriate antibiotics.

Differentiation between dietetic and infective diarrhoea is admittedly difficult but the former never appeared to be an important cause of illness. Those patients given supplementary protein did not suffer an obvious increase in diarrhoea.

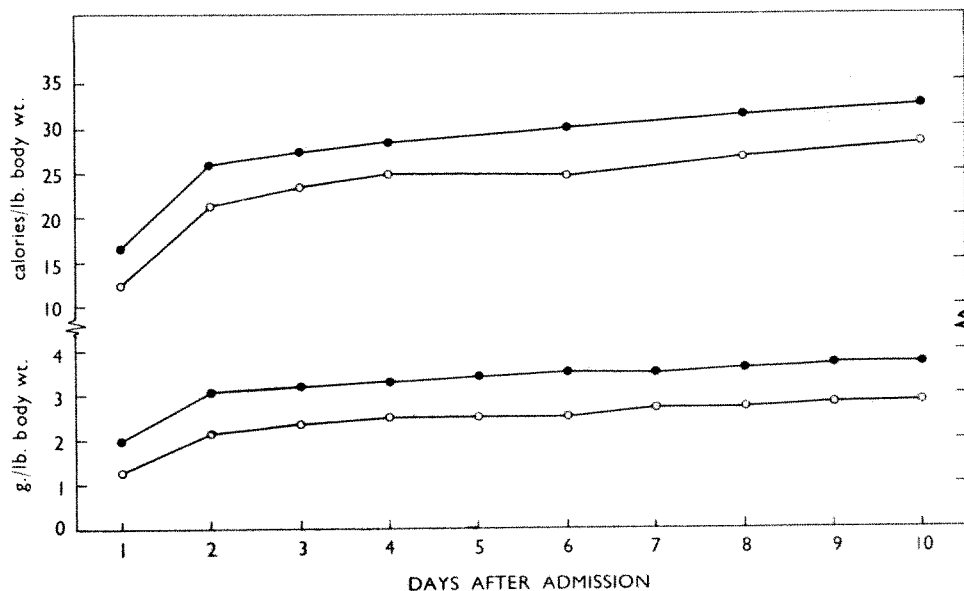


FIG. 1.—Mean calorie and protein intakes of both groups.
○ = SLAM: skimmed lactic acid milk; ● = SLAM + PS: skimmed lactic acid milk plus protein supplement.

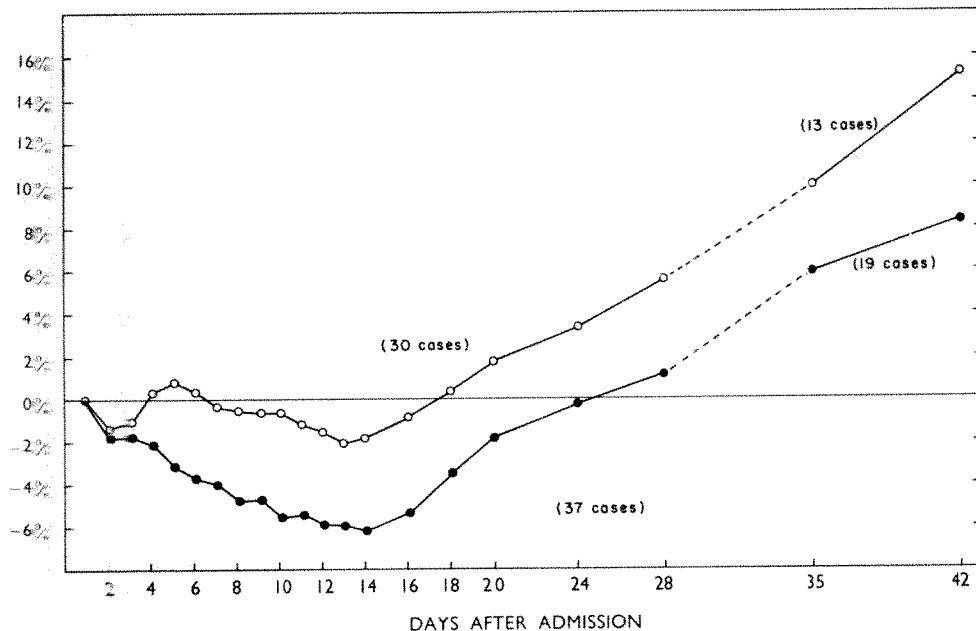


FIG. 2.—Mean percentage change in body weight in both groups.
○ = SLAM; ● = SLAM + PS.

Protein Intake. (Fig. 1.) By the 10th day of treatment the mean protein intake of the SLAM + PS group was 30% more than in the SLAM group (3.7 g. as compared with 2.8 g./lb. body weight).

Caloric Intake. (Fig. 1.) Likewise by the 10th day of treatment the mean caloric intake of the SLAM + PS group was higher than in the SLAM group (32.5 as compared with 28.4 cal./lb. body weight).

Weight Change. The percentage change in body weight (Fig. 2) in the two groups showed that those given protein supplement did not gain as well as those fed skimmed milk only. By the 28th day, the SLAM + PS group was only about 1% above their admission weight, but the SLAM group (without supplement) was 5.6% over the admission weight. This difference was probably significant ($p < 0.05$).

In the second series of cases which were weighed up to 42 days, there was still a difference between

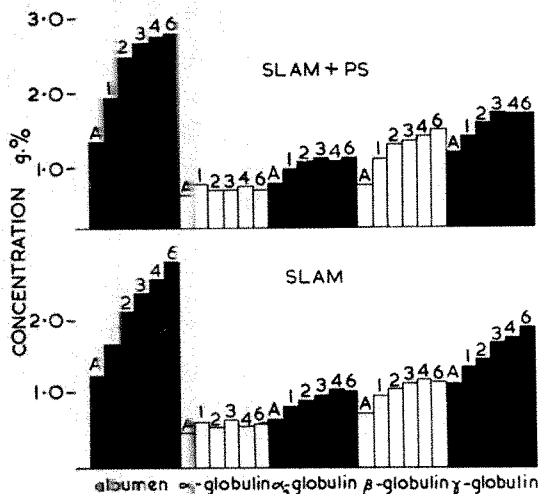


FIG. 3.—Mean serum proteins and fractionation in both groups.
A = on admission; numerals refer to number of weeks after admission.

TABLE 2

Cases	Treatment	
	SLAM	SLAM + PS
Mean weight (lb.):		
On admission	19.3	20.0
At 28 days	20.5	20.2
At 42 days	22.4	21.6
Mean protein intake at 10 days (g./lb. body weight)	2.8	3.7
Mean caloric intake at 10 days (cal./lb. body weight)	28.4	32.5

the two groups, but this was no longer significant (Fig. 2).

Serum Proteins. Fig. 3 compares the serum protein levels of the two groups. There was no greater rise in those cases receiving protein supplement.

Discussion

Adequate control groups are essential when a trial of varied treatments is undertaken. In this investigation random allocation of cases resulted in similar age and weight distributions and severity of kwashiorkor in the two treatment groups. Thus the only difference between the groups was the diet.

We have used weight gain, a rise in serum proteins and clinical recovery as the criteria for improvement in the two groups. When observed for only 28 days those patients receiving supplementary protein did not gain as well as those receiving skimmed lactic acid milk only (Fig. 2). When, however, the patients were observed for 42 days, this difference was much less evident. Possible reasons for this difference are the slightly larger number of infections in the first week and the earlier loss of oedema in this group. Alternatively, it may be due to difficulty experienced in metabolizing the extra protein. The amount of protein taken increased daily so that by the 10th day a mean of 2.8 g. per lb. body weight daily was consumed by the control group. This was sufficient to initiate cure as defined by Brock, Hansen, Howe, Pretorius, Davel and Hendrickse (1955). It is felt therefore, that supplementation of skimmed milk with extra protein is unnecessary. This merely confirms the opinion of Pretorius *et al.* (1956), Pretorius and Smit (1958), and Béhar, Viteri, Bressani, Arroyave, Squibb and Scrimshaw (1958).

Sénécal (1958), on the other hand, has recently reported excellent results with partly skimmed milk supplemented by protein hydrolysates, but his conclusions are not supported by a controlled series of patients. He felt that his good results were due in part to the high caloric intake, 25% of which was supplied by protein. His patients took as much as 140 calories per kg. per day. In our patients no attempt was made to increase the caloric intake above that provided by skimmed milk (and extra protein), recovery occurring on 55-65 calories per kg. per day. In patients developing kwashiorkor, it is believed that the caloric intake is adequate but that protein is markedly deficient. In Sénécal's cases, one suspects that some patients were marasmic and deficient in both calories and protein. We realize, however, that the earlier introduction of a ward diet is likely to be of benefit to some patients,

and that 14 days on skimmed milk only is probably too long.

We are convinced that infection plays an important part in retarding the recovery of our patients and in the causation of a mild but persistent anaemia, as has already been suggested by Walt (1959). Although it is difficult to assess, we believe that the prophylactic penicillin and sulphonamides used in this trial were of no obvious benefit. We feel therefore that chloramphenicol is probably the drug of choice, particularly in our area where infective enteritis is common.

The total serum proteins and all fractions increased rapidly by the 14th day of the treatment; thereafter they rose only a little more to levels and ratios typical for African patients. We are at variance with Sénécal (1958), who despite a statement that the α_2 globulin decreases, produced a diagram remarkably similar to our Fig. 3. In all our cases this fraction rose steadily and rapidly.

Conclusions

In this series of patients no advantage in weight gain was demonstrated in those receiving protein supplements and therefore higher caloric intake. The minimum quantity of protein, on a body weight basis, necessary for the cure of kwashiorkor has yet to be determined, even though Dean (1953) stated that he had had some good results from as little as 25 g. protein daily. In this series, by the 10th day, 2.8 g. per lb. body weight, representing more than 50 g. protein in the average patient, was consumed and cure was initiated. It is possible that some patients would profit even more by the introduction of a full ward diet as early as the eighth day.

Because infection plays a major role in the early deaths from kwashiorkor, a series of cases receiving a broad spectrum antibiotic prophylactically needs to be studied.

We believe that 'pure' or uncomplicated kwashiorkor responds so well to skimmed cow's milk that these patients should never die. Skimmed milk is very satisfactory and much cheaper than protein hydrolysates or concentrated powdered milk protein, which have not yet been shown to be superior. The rightful place of skimmed milk appears to be as a supplement to the high carbohydrate (starch) diet of the African. Although 'Tervamix' has not been shown in this study to hasten the cure of patients with overt kwashiorkor, it may well be a useful non-bulky high protein supplementary food.

Summary

The treatment of two groups of patients with kwashiorkor is compared. Both received skimmed

lactic acid milk but one group was supplemented with concentrated milk protein.

This group did not show any advantage in clinical recovery, weight gain or rise in serum protein levels over the non-supplemented group.

It is concluded that protein supplementation of skimmed milk in the treatment of kwashiorkor is not beneficial.

Our thanks are due to Dr. Alan Taylor, Medical Superintendent, McCord Zulu Hospital, for facilities; to Dr. S. M. Joubert, Pathologist, Faculty of Medicine, University of Natal, for the serum protein estimations and Fig. 3; to Drs. L. Robertson and S. A. Randeree, Paediatric Registrars, for their care of the patients and records. The folic acid used ('Folvite') was generously donated by Lederle Laboratories Division, American Cyanamid Company; the 'Imferon' by Bengel Laboratories, London, and the 'Tervamix' by Tervalon Ltd., Utrecht, Holland.

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THE NATURE OF THE NEONATAL PULMONARY HYALINE MEMBRANE

BY

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Hyaline membranes are seen in the lungs of nearly one-third of prematurely born infants who die after birth at the Royal Women's Hospital, Melbourne. The nature of the membranes has been discussed often in the literature (Farber and Wilson, 1932; Tregillus, 1951; Claireaux, 1953; Bruns and Shields, 1954; Gilmer and Hand, 1955; Lendrum, 1955; Lynch and Mellor, 1955; Stevenson and Laufe, 1955; Gitlin and Craig, 1956 and many others). The subject has also been reviewed by Tran-Dinh-De and Anderson (1953), Curtis (1957), and others, and in an Editorial in the *Lancet* (1958). So far there is no generally accepted explanation of the mode of origin of the membranes and opinions differ widely on the nature of the material of which they are composed. Two main views are held. One postulates an origin from the contents of the amniotic sac and the other from an exudate from the pulmonary capillaries.

The present study is based on observation of morphological changes in affected lungs and was undertaken after a variety of histochemical and interferometric techniques had been employed without significant result. From microscopic examination of the lungs using sections prepared by conventional methods it is concluded that hyaline membranes result from necrosis of epithelial cells in respiratory bronchioles and form *in situ*.

Material

Sections of the lungs have been examined from 133 consecutive cases of hyaline membrane disease occurring in a three-year period and the clinical notes of each case have been reviewed. Necropsy is routine for infants who die and only very rarely is objection made. Approximately 320 autopsies (stillbirths and neonatal deaths) are performed each year. Blocks are taken from the lower lobe of one lung in every case, fixed in formalin and prepared for microscopic examination in the usual way. Sections are cut from one block in each case.

Microscopic Findings. Most hyaline membranes are of a uniform eosinophilic and homogeneous appearance and line air spaces which appear to have been patent at the time of death. The affected air spaces are usually described as alveolar ducts and sometimes as alveolar ducts and alveoli. It is now clear that the alveolar components of the lungs are not involved in hyaline membrane disease and that respiratory bronchioles are the site of hyaline membrane formation.

In sections stained to show elastic fibres the characteristic pattern for respiratory bronchioles is seen around all hyaline membrane affected spaces (Fig. 1). Between affected spaces the lung has a solid structure in which elastic fibres are less frequent, stain faintly and are of irregular distribution. Frequently hyaline membranes are seen lining one side of a respiratory bronchiole while the opposite side is lined normally by cuboidal epithelial cells. In some cases hyaline membranes are seen in longitudinal sections of respiratory bronchioles abutting on the normal columnar lining of terminal bronchioles. Spaces lined by membranes usually have a surrounding lamina propria outside which there are obvious respiratory structures of smaller dimension which are not patent. These are the definitive alveolar tissues in which hyaline membranes do not occur.

In the immature lung of the 1,001-1,500 g. baby the general anatomical features seem to us to be as illustrated in Fig. 2.

T is a terminal bronchiole around which the elastic layer is continuous. R_1 and R_2 are respiratory bronchioles around which the elastic layer is interrupted. A is a site containing potential alveolar tissues which may or may not be functional at this stage of development. Here the elastic fibres have no pattern and are less numerous.

The transition from a terminal to a respiratory bronchiole is abrupt. The columnar cells of the terminal bronchiole give way to much less con-



FIG. 1.—Section of respiratory bronchiole showing interrupted pattern of elastic fibres.
(Weigert's elastic stain $\times 228$.)

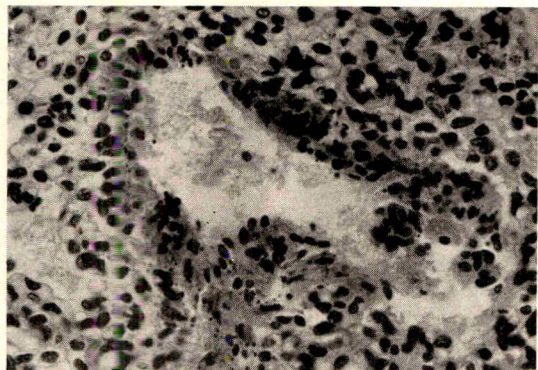


FIG. 3.—Section of respiratory bronchiole lined by partly necrotic epithelial cells.
(H. and E. $\times 228$.)

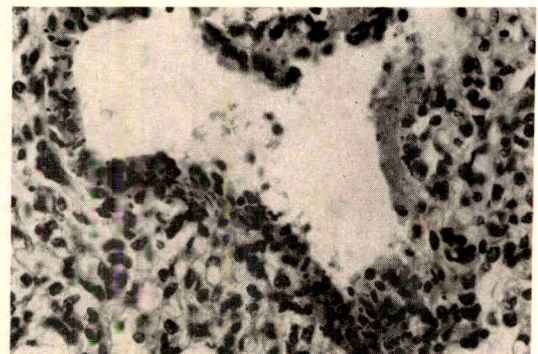


FIG. 4.—Section of respiratory bronchiole showing partly necrotic epithelial cells and a segment of hyaline membrane on the right.
(H. and E. $\times 228$.)

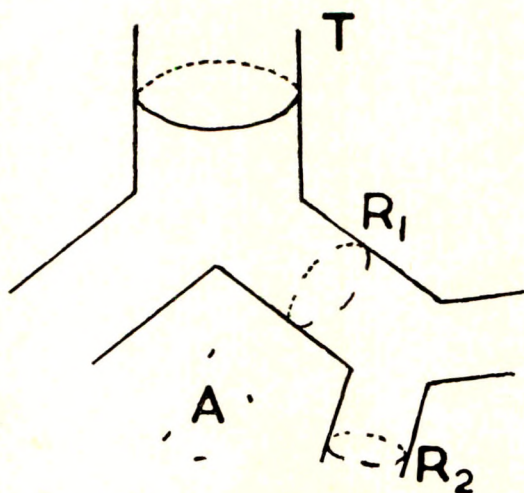


FIG. 2.—Diagrammatic illustration of elastic fibres around bronchioles.

spicuous epithelial cells which are cuboidal or lower. The elastic layer becomes interrupted and the lumen is narrower. The cuboidal cells lining respiratory bronchioles have a clear colourless cytoplasm and a centrally placed round vesicular nucleus.

In 69% of the cases in this series the membranes were not all entirely eosinophilic but contained basophilic particles. In some cases these stained deeply while in others they were just visible. Sometimes the origin of the basophilic particles from the nuclei of epithelial cells was obvious (Fig. 3) mainly because of the regular distribution around the lumen and also because of the size and location of the material in relation to the surrounding eosinophilic membrane. Except when the particles were extremely fragmented there was no possibility of mistaking the appearances for degenerate leucocytes. Appreciation of the epithelial origin of the lesion depicted in Fig. 4 led to detailed examination of all sections, membrane by membrane, in order to follow the changes by which membranes result from degeneration of epithelial cells.

The first changes observed occur simultaneously in cytoplasm and nucleus. The cytoplasm swells slightly and becomes eosinophilic and the nucleus loses its vesicular appearance and soon becomes pyknotic (Fig. 5). Later there is an enormous increase in the size of the cell and an increase in eosinophilia. The nucleus elongates or fragments and is either passed out of the cell or blends with the cytoplasm. Finally, distinction between the cells becomes difficult except on the luminal aspect of the membrane which is somewhat irregular. This

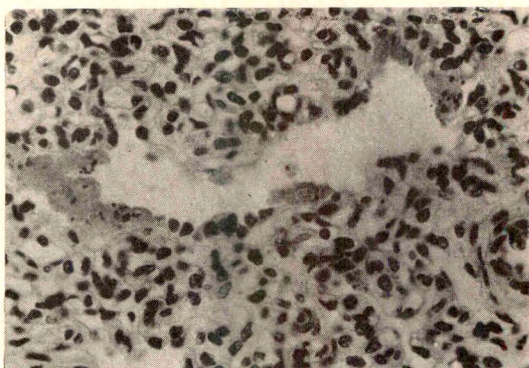


FIG. 5.—Section of respiratory bronchiole showing intact epithelial cells flanked by hyaline membrane. Some nuclei are pyknotic and others in the membrane are fragmented.
(H. and E. $\times 228$.)

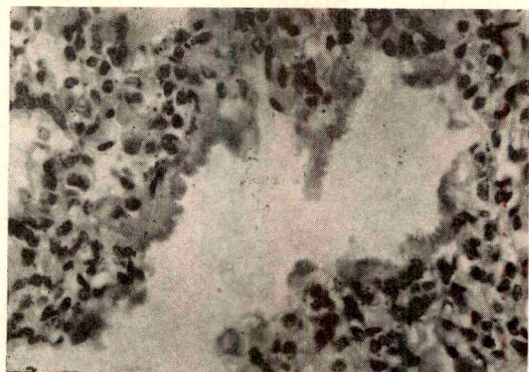


FIG. 6.—Section of respiratory bronchiole showing typical hyaline membrane and characteristic irregular edge.
(H. and E. $\times 228$.)

irregularity often accurately reflects the margins of the original cells (Fig. 6).

Clinical Features

The 133 cases resulted from 121 pregnancies. There were 67 male and 66 female infants. Nearly all died between two and 48 hours after birth (Fig. 7) and the majority died in the first 16 hours.

One hundred and twenty-three infants were premature, 10 weighed over 2,500 g. and one of these was postmature (Fig. 8). Infants below 1,000 g. showed pulmonary hyaline membranes, but the majority of the cases occurred in the 1,001-2,000 g. range.

The incidence of the lesion is inversely proportional to the gestational age and 60% were asphyxiated at birth (Fig. 9). Asphyxia is defined as taking two minutes or more to establish rhythmical respirations after delivery and most of these infants received lobeline and/or coramine. In 60% of cases it was

recorded that oxygen was administered at delivery, usually by an intranasal catheter. This is a common procedure in our hospital for prematurely born infants and the actual number so treated is higher than recorded. Asphyxia at birth was more common in infants born at 34 weeks and over (76%) than in the group under 34 weeks (54%).

Of the 24 infants delivered abdominally, 20 (83%) were asphyxiated at birth and usually severely. This incidence of asphyxia is higher than for the series as a whole and suggests that it is asphyxia in cases delivered by caesarian section and not this mode of delivery *per se* which is the important factor in the subsequent development of hyaline membrane disease. In 32% of cases delivery was by breech.

The complications of pregnancy, apart from maternal diabetes, were those associated with premature delivery although the individual incidences were greater than expected in premature deliveries as a whole (Table 1). There were 24 multiple pregnancies. In 11 (10 twin, one triplet), all the infants died and showed hyaline membranes at autopsy. In 12 multiple pregnancies (11 twin, one triplet), only the second twin or third triplet was affected.

Nearly one half of the infants who died in the 1,001-2,000 g. group showed hyaline membrane formation (Table 2) but the maximum incidence occurred in the 1,001-1,500 g. group.

In 61% of the cases pulmonary hyaline membranes were the only major findings at necropsy.

The condition of the infants was poor from birth and signs of respiratory distress developed rapidly. In most infants there was no period of well-being. Lateral chest and lower sternal retraction occurred early and became progressively more severe. An expiratory grunting cry was easily heard. The four limbs often assumed an abducted and externally rotated position. Apnoeic attacks with cyanosis occurred with increasing severity. On auscultation

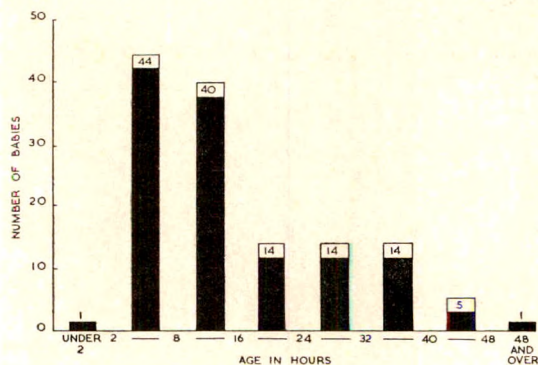


FIG. 7.—Age of infants at death.

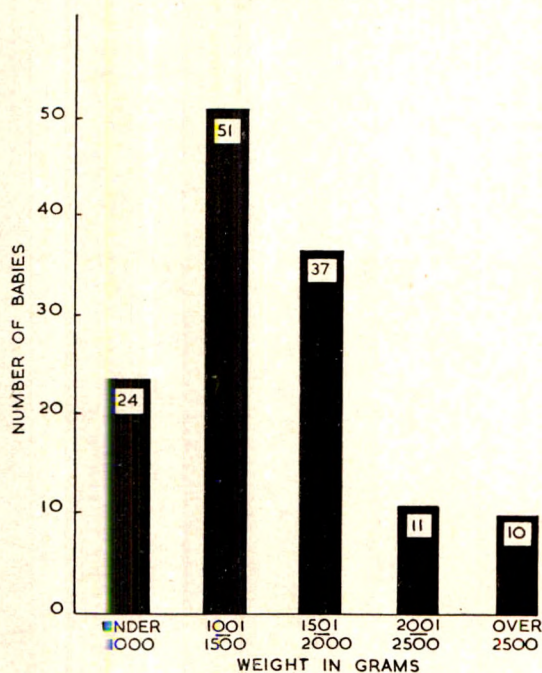


FIG. 8.—Birth weight.

the only constant finding was poor air entry into the lungs.

Discussion

The origin of hyaline membranes in infants from necrosis of epithelial cells in respiratory bronchioles

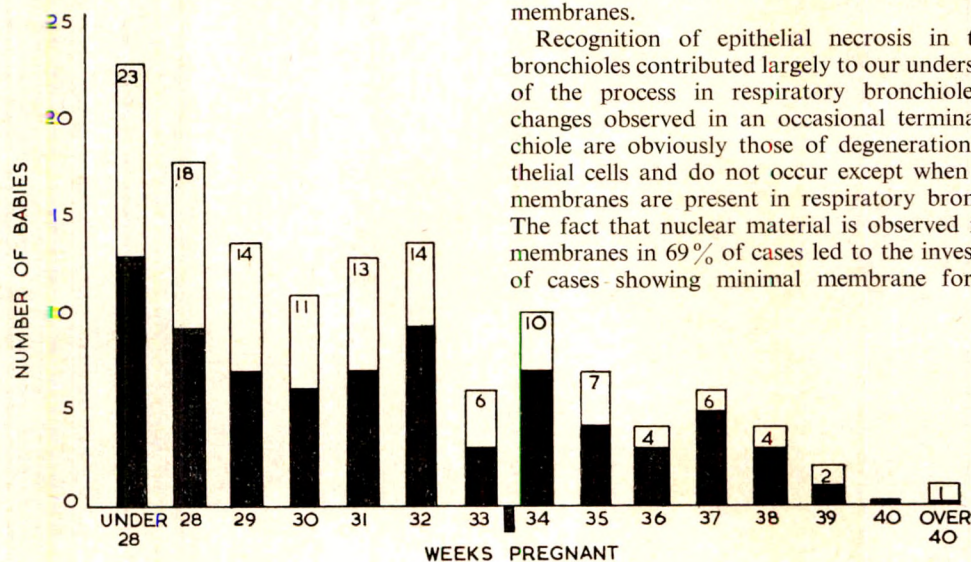


FIG. 9.—Gestational age; ■ = number asphyxiated at birth.

TABLE 1
COMPLICATIONS OF PREGNANCY

Multiple	24	20%
Pre-eclampsia	18	17%
Eclampsia	2	9%
Accidental haemorrhage	11	8%
Placenta praevia	10	6%
Diabetes	7	

TABLE 2
BIRTH WEIGHT, NEONATAL DEATHS AND HYALINE MEMBRANE INCIDENCE

Weight (g.)	Neonatal Deaths	Hyaline Membrane	
		Nos.	Incidence per 1,000 Live Births
Up to 1,000	184	24	125
1,001-1,500	122	51	204
1,501-2,000	71	37	78
2,001-2,500	47	11	11
Over 2,500	96	10	0.5

has not been so described until recently (Barter, 1959). Tregillus (1951) showed lesions in the epithelial linings of terminal bronchioles but did not state clearly the relationship of such lesions to hyaline membranes; nor did he appear to appreciate that the principal lesion is confined to respiratory bronchioles. Lynch and Mellor (1955) using histochemical methods have hinted at a relationship between membranes and bronchiolar epithelial cells but so far have come to no definite conclusions about the nature of the disease. However, they have shown similar histochemical properties between epithelial cells in the respiratory tract and hyaline membranes.

Recognition of epithelial necrosis in terminal bronchioles contributed largely to our understanding of the process in respiratory bronchioles. The changes observed in an occasional terminal bronchiole are obviously those of degeneration in epithelial cells and do not occur except when hyaline membranes are present in respiratory bronchioles. The fact that nuclear material is observed in some membranes in 69% of cases led to the investigation of cases showing minimal membrane formation.

All stages of epithelial necrosis from nearly intact cells to those containing faint remnants of nuclei can be observed in many of these cases. That these are the nuclear remnants of epithelial cells is evident from studying all the phases of the degenerative process. It has become clear that epithelial cell necrosis is the basis of hyaline membrane formation and that lesions are found in both terminal bronchioles and respiratory bronchioles but mainly in the latter. The epithelial linings of the trachea and bronchi are not affected and we have found no evidence that membranes form in alveolar ducts or alveoli. Furthermore, it seems likely from our own unpublished observations that alveolar tissues are not as well developed in the premature lung as commonly implied.

Much of the controversy at present about the nature of hyaline membranes centres on the assumption that the material present is derived from substances in the air spaces or from the pulmonary capillaries. Considerable evidence has been presented in favour of one or both explanations. Farber and Sweet (1931) first proposed an origin from the contents of the amniotic sac and changed the name of the lesion, hyaline membrane (Johnson and Meyer, 1925) to vernix membrane. Claireaux (1953) published the results of experimental studies in favour of an origin from aspiration of epidermal material. More recently it has been suggested that thromboplastic substances from the liquor aid in the formation of fibrin from an exudate from the capillaries (Laufe and Stevenson, 1954).

Emphasis has been placed on the exudate hypothesis by the claims of Gitlin and Craig (1956) that membranes are composed largely of fibrin. These workers used a fluorescein labelled antibody for fibrin and showed that membranes in treated sections were brightly fluorescent. Confirmation of the presence of fibrin has been afforded by van Breemen, Neustein and Bruns (1957) who studied thin sections of membranes with an electron microscope. Brown (1959) has stated that the evidence for fibrin is incontrovertible. It should be realized, however, that neither of the techniques proves that the membrane consists of nothing but fibrin. The presence of some of it is not disputed, but we believe that it results from exudation after loss of the normal epithelial lining and is only a small component of the membrane.

The reported incidence of hyaline membranes from different centres shows some variation but there is a remarkable difference between that in South India (Hadley, Gault and Graham, 1958) or Vietnam (Tran-Dinh-De, 1959) and, for example, Melbourne. Thus Hadley *et al.* found only

one case in 215 neonatal deaths and from discussion with Tran-Dinh-De we estimate our incidence to be some 20 times greater than his. At present there is no explanation for these differences.

Experimental methods have not reproduced the disease in a manner corresponding to its occurrence in the human. Bruns and Shields (1954) have, however, produced what are apparently hyaline membranes in the guinea-pig lung after prolonged exposure to oxygen. These workers state that the membranes form as a result of epithelial necrosis in bronchioles. Their observations on the derivation of membranes so produced is in accord with our own in premature infants.

It is attractive to suggest that a noxious substance is the cause of the necrosis in this disease but the evidence for oxygen poisoning in the human premature infant, exposed for short periods, is incomplete.

Summary

Detailed microscopic study of the lungs of premature infants affected by hyaline membrane disease shows that the membranes result from epithelial cell necrosis in respiratory bronchioles and form *in situ*.

A description of 133 cases of hyaline membrane disease including clinical features is presented.

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PATENT DUCTUS ARTERIOSUS IN INFANCY

BY

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In a report on 1,000 autopsies performed on patients dying of congenital heart disease, Abbott (1937) found that the principal lesion was a patent ductus arteriosus in 282 patients; 20% of these were infant deaths.

Subsequently numerous reports have stressed that while this abnormality can prove fatal during the first year of life, surgery in skilled hands offers an effective remedy at this age with negligible risk (Ziegler, 1952; Rudolph, Mayer, Nadas and Gross, 1958; Bauersfeld, Adkins and Kent, 1957).

Accurate diagnosis, however, may be difficult in infants. The classical continuous murmur so frequent in the older child (Hay and Ward, 1956) may not be heard, and interpretation of the signs which do present is not easy. In addition, the many complex cardiac abnormalities which are seen in infants give rise to special problems in differential diagnosis.

In this paper the clinical findings and results of ancillary investigations are analysed in 28 infants in whom patent ductus arteriosus was the sole cardiac lesion.

Clinical Findings

Symptoms and Physical Signs. The principal features of each case are set out in Table 1. Twenty-three babies presented with dyspnoea and 21 had had bronchitis. Recurrent respiratory infections often severe and accompanied by marked breathlessness caused concern in 13 babies (46%); dyspnoea, accentuated by feeding or crying, was common in this group and all 13 were under weight when first seen.

Heart failure as evidenced by peripheral oedema, hepatomegaly and lung crepitations occurred in four cases (Cases 1, 2, 11 and 14); in three it was precipitated by bronchopneumonia.

The 'waterhammer' character of the pulse was noted in all cases and often provided the first clue to the diagnosis. It was not always easily detected at the wrist, particularly in the restless infant, but was always readily felt in the tibial vessels at the

ankle. In 17 infants (60%) the waterhammer quality was very impressive.

A systolic thrill was noted in 12 cases (43%) and this was usually localized to the pulmonary area. A murmur which began after the first sound and which extended through the second sound into diastole was audible in 22 babies (78%). The classical 'machinery' quality was rare, though a low-pitched systolic rattle was often heard. The murmur extended into diastole for a variable period but was seldom as long as the typical murmur in older children. We have, nevertheless, defined this murmur as being continuous because it continues through the second sound from systole into diastole as Gibson (1900) originally defined it. The continuous murmur was confined to the second left intercostal space, but the systolic element was widely conducted and sometimes even louder in the third or fourth left intercostal spaces close to the sternal edge. In the remaining six cases a continuous murmur was not present and the point of maximal intensity of the systolic murmur was difficult to determine. An independent apical mid-diastolic murmur was recorded in 18 infants (64%). Four of these had no continuous murmur and the diastolic murmur was the most striking one; catheterization was done in three of these four cases and all three had marked pulmonary hypertension.

Radiography. Standard antero-posterior and oblique films were taken in all cases. Pulmonary plethora associated with some degree of cardiac enlargement was present in all. The cardiac contour was not in any way characteristic, though 14 infants (50%) showed a well-defined pulmonary arc. Selective enlargement of the left ventricle was suggested in 18 (64%), and of the left atrium in seven (25%).

Electrocardiography. Standard and unipolar limb leads as well as four precordial leads (V3R, V1, V3 and V6) were recorded in all cases. Interpretation was based on Ziegler's (1951) criteria.

Case No.	Age	Symptoms			Signs				Radiograph	
		Dyspnoea	Bronchitis	Heart Failure	Thrill	C.M.	M.D.M.	B.P.	C.T. ratio	L.A.
1	12 days	++	++	+	+	0	+	95 syst.	0.7	N
2	24 days	+	+	+	0	+	+	100/0	0.68	+
3	7 weeks	++	++	0	+	+	+	100/0	0.66	N
4	8 weeks	++	+	0	0	+	+	110/40	0.6	N
5	3 mths	++	+	0	0	+	0	85 syst.	0.67	+
6	4 mths	++	++	0	0	0	+	75 syst.	0.63	N
7	4 mths	+	+	0	0	+	+	120/55	0.65	+
8	5 mths	++	0	0	+	+	+	105/0	0.67	+
9	5 mths	++	+	0	0	+	0	not recorded	0.6	N
10	5 mths	++	+	0	0	+	0	80/0	0.56	N
11	5 mths	++	0	+	0	+	+	120/70	0.67	N
12	5 mths	+	+	0	+	0	0	not recorded	0.6	N
13	5 mths	+	0	0	0	+	0	115/75	0.62	N
14	5 mths	++	++	+	0	0	+	not recorded	0.63	N
15	6 mths	++	++	0	0	0	0	110/70	0.58	N
16	6 mths	0	+	0	+	+	+	95 syst.	0.59	+
17	6 mths	++	++	0	+	0	+	95/10	0.61	N
18	6 mths	0	+	0	+	+	+	120/60	0.62	N
19	7 mths	++	0	0	+	+	+	110/60	0.7	N
20	8 mths	+	++	0	0	+	0	not recorded	0.6	N
21	9 mths	0	++	0	0	+	0	100/0	0.6	N
22	9 mths	+	0	0	0	+	+	120/70	0.8	+
23	9 mths	+	+	0	0	+	+	100/0	0.64	+
24	10 mths	+	0	0	0	+	0	100/0	0.6	N
25	10 mths	++	++	0	+	+	+	115/55	0.64	N
26	11 mths	+	+	0	+	+	0	120/70	0.59	N
27	11 mths	0	++	0	+	+	+	95/45	0.58	N
28	12 mths	0	0	0	+	+	+	not recorded	0.57	N

Notes: C.M. = Continuous murmur.

M.D.M. = Mid-diastolic murmur.

B.P. = Blood pressure.

Vertical or semi-vertical electrical position was usual: only one horizontal heart was found. The electrical axis was normal in 23 (82%), four showed right axis deviation and one left axis deviation. There was evidence of left atrial enlargement in four patients. In 13 (46%) ventricular activity was normal. Left ventricular hypertrophy was evident in 11 records (40%), always with an isoelectric S.T. segment and a normal upright T wave in the left ventricular leads. Combined right and left ventricular hypertrophy was recorded in four cases (14%) while isolated right ventricular hypertrophy was present in only one (Case 19).

A pattern consisting of large RS deflections over the right ventricle with normal activity in left ventricular leads and deep Q waves in leads 111 and aVF was recorded in eight cases (28%). In all of these the duct measured 7 mm. or more (Cases 1, 6, 8, 11, 12, 15, 22 and 28) and in three there was marked pulmonary hypertension (Cases 1, 6 and 15).

The prevalence of deep Q waves in this series was an interesting feature. They were invariably present in lead V6, measuring 3 mm. or more in 12 instances (43%). Twenty-three infants (80%) showed a deflection of 3 mm. or more in either lead

Electrocardiogram										Age at Operation (mths)	Diameter of P.D.A. (mm.)
aVF			V3R		V1		V6				
R	Q	R	R	S	R	S	Q	R	S		
9	2.5	5	15	16	15	16	1	4	11	24	14 divided
14	2	12	4	2	12	8	1	14	10	2	6
1	1	3	20	27	24	25	3	11	0	3	5
12	3	11	7	2	8	1	3	19	0	9	6
9	2	13	8	7	8	8	1	15	0	4	5
13	5	10	18	22	18	24	1	13	0	13	7
10	0.4	15	7	15	14	28	2	23	0	5	7
13	4	15	11	11	15	14	2	15	0	5½	7
10	3	6	14	0	5	0	1	13	0	Died at 6½ mths; autopsy	5
20	4	15	14	0	12	8	1	15	1	9	6
16	17	9	20	22	15	22	2	14	0	5	9 divided
6	8	12	24	34	23	34	4	5	0	Died at 11 mths; autopsy	7
11	2	10	8	13	8	20	10	34	0	7 yrs.	7
12	6	11	18	3	14	5	1	8	7	Died at 12 mths; autopsy	15
14	9	10	24	23	23	24	8	8	0	14	14
17	10	15	14	14	13	19	1	23	0	27	7
15	4	15	1	13	1	13	2	23	—	9	10
5	1	9	10	10	18	19	1	11	—	12	6.5
2.7	0	4	13	1	26	0.2	1	7	13	Died at 7 mths; no autopsy	—
14	2	12	5	6	3	5	2	14	0	12	6
14	2.5	15	5.5	9	5	10	3	17	0	13	6.5
12	4	12	12	11	12	15	6	16	0	9	9
40	14	26	8	12	9	12	8	35	0	11	6
11	1	12	9	8	7	9	3	23	0	4½ years	10
7	2	11	10	13	9	9	5	29	0	14	5
12	3	14	11	16	8	20	5	20	0	11	6
10	5	10	6	8	5	10	1	12	0	13	7
12	5	9	10	7	8	8	4	13	0	12	7

Ratio = Cardio-thoracic ratio.

L.A. = Left atrium.

L.V. = Left ventricle.

P.D.A. = Patent ductus arteriosus.

111 or aVF. The amplitude of the QRS complexes in leads 111, aVF, V3R, V1 and V6 are tabulated (Table 1).

Special Investigations. Cardiac catheterization was performed in four of the 28 infants (Cases 1, 6, 15 and 17) in whom the diagnosis remained uncertain after clinical, electrocardiographic and radiographic examination (Table 2). All had marked pulmonary hypertension and in three (Cases 1, 6 and 15) the greatest difference between the pulmonary artery and aortic pressures during sedation was 4 mm. Hg. In one of these there was

evidence of a left to right shunt through the ductus but in the other two the diagnosis was confirmed by passing the catheter into the descending aorta.

Venous angiocardiology was carried out in one (Case 3) when the catheter could not be advanced into the pulmonary artery. This showed dilatation of the left pulmonary artery with dilution of the contrast medium in the artery at the site of entry of the patent ductus.

Treatment

When heart failure was present it was treated with digoxin and diuretics. Pulmonary infections

TABLE 2
CARDIAC CATHETERIZATION

Cases	Oxygen Saturation (%)			Pressures in mm. Hg		Diameter of Ductus (mm.)	Fall in Pressure in Pulmonary Artery after Clamping Ductus (mm. Hg)
	S.V.C.	P.A.T.	Aorta	P.A.T.	Aorta		
1 (R.D.)	63	63	80	94	98	14	34
6 (I.W.)	46	54	59	62	60	7	10
15 (S.B.)	58	58	69	88	92	14	14
17 (R.W.)	50	84	not entered	58	58	10	not measured
				132	130		
				80	70		
				84	not entered		
				44			

S.V.C. = Superior vena cava

P.A.T. = Pulmonary artery trunk

were treated with antibiotics. All the patients responded satisfactorily to treatment and operation was never performed in the presence of heart failure or infection.

The ductus was either ligated or divided, depending on its size, in 24 of the 28 infants. There were no deaths and closure was incomplete in only one infant in whom the duct was found to be broad and frail. The age at operation and minimum external diameter of the ductus is tabulated (Table 1).

The remaining four infants (Cases 9, 12, 14 and 19) died while awaiting admission for further assessment and operation. Two of these had other serious abnormalities (one, Case 14, had Albers-Schönberg's disease, and the other, Case 9, had Möbius' syndrome); one, Case 19, developed fulminating gastroenteritis, and the fourth baby, Case 12, developed bronchopneumonia at home and died.

Differential Diagnosis

In the majority of infants patency of the ductus may be differentiated from other lesions with confidence after clinical examination, radiography, electrocardiography and phonocardiography. In some babies, on the other hand, a large patent ductus may present without any of the typical signs and differential diagnosis is difficult. The lesions with which patent ductus arteriosus is most commonly confused in the early months of life are persistent truncus arteriosus and ventricular septal defect. Another important consideration is that a patent ductus may be compensating for a more serious underlying lesion and this possibility must always be borne in mind.

The following case summaries are detailed to illustrate the problems involved in the diagnosis of patent ductus arteriosus. The first two cases (Case 2 and Case 1) show that the clinical picture of a small ductus without pulmonary hypertension differs widely from that of a large ductus with

pulmonary hypertension at systemic level. The third case shows how even when the ductus is compensatory it may dominate the clinical picture.

The fourth case shows how closely persistent truncus arteriosus may resemble patent ductus arteriosus in the first few months of life.

B.L. Case 2. Small patent ductus. Normal delivery followed an uncomplicated pregnancy. The birth weight was 7 lb. 4 oz. Bronchopneumonia at 2 weeks of age led to admission to hospital, where heart failure was diagnosed in addition to pneumonia. Improvement followed therapy with penicillin and digoxin. He was transferred to this clinic when 3½ weeks old. At that time he weighed 5 lb., was poorly nourished and had slight dyspnoea at rest. There was a waterhammer arterial pulse and a continuous murmur in the pulmonary area with an independent apical mid-diastolic murmur. Phonocardiography showed that the murmur began after the first sound, reached a late systolic crescendo and extended without interruption into early diastole (Fig. 1). Both aortic and pulmonary valve closure were clearly recorded in the second left intercostal space. The heart was enlarged radiologically (C.T. ratio 0.68) with selective enlargement of the left atrium and there was pulmonary hyperaemia. The electrocardiogram was normal.

At thoracotomy a patent ductus arteriosus of minimal external diameter 6 mm. was transixed and ligated. Progress since then has been entirely satisfactory. The child is gaining weight well and has no dyspnoea. His heart sounds are normal and there are no murmurs.

COMMENT. In this case the clinical, radiographic, electrocardiographic and phonocardiographic appearances were typical of a patent ductus which was confirmed at thoracotomy.

R.D. Case 1. Large patent ductus arteriosus with marked pulmonary hypertension. This male infant was born by normal delivery after eight months of uncomplicated pregnancy and weighed 5 lb. 13 oz. at birth. Normal respirations developed spontaneously and his general condition seemed satisfactory. Heart failure developed on the third day of life and a loud systolic murmur was noted.



FIG. 1.—Phonocardiogram recorded from second left interspace showing continuous murmur with late systolic accentuation.

When first seen at this clinic on the 12th day of life, his condition had improved following digoxin therapy though dyspnoea and moderate oedema of the extremities persisted, and some fine crepitations were noted at the base of the right lung. The arterial pulses were regular and of 'full' volume. A long systolic murmur of low-pitched blowing quality was heard in the pulmonary area and down the left sternal edge, the point of maximum intensity being uncertain. No diastolic murmur was heard.

Radiography showed marked generalized cardiac enlargement and increased pulmonary vascularity.

Electrocardiography showed right axis deviation, a vertical heart and large R/S deflections over the right ventricle (R V3R 15 mm., S V3R 16 mm.). In the left ventricular leads tall T waves suggested left ventricular

diastolic overload, though the height of the R waves were within normal limits (R V6 4 mm.). A provisional diagnosis of ventricular septal defect was made.

PROGRESS. The signs of congestive failure gradually disappeared with continued digoxin therapy. Dyspnoea persisted and at 6 weeks the infant weighed only 5 lb. 10 oz. He was seen regularly in the clinic and his progress over the next two years was punctuated by monthly attacks of bronchitis, occasional cyanotic episodes, usually associated with feeding difficulties, and persistent moderate dyspnoea at rest. He gained weight slowly and was only 23 lb. at 2 years. He did not stand with support until he was 2 years old and had not begun to walk at that age. The clinical signs in the cardiovascular system varied little throughout this period. The arterial pulses were always of full volume and a waterhammer quality was occasionally recorded. The systolic murmur persisted and latterly was accompanied by a faint systolic thrill in the second and third left intercostal spaces. The second sound in the pulmonary area was accentuated and finely split.

Cardiac enlargement was a constant radiological finding but became relatively less marked with age. The pulmonary arc became more clearly defined after the second month. A moderate degree of pulmonary plethora persisted.

In the electrocardiogram the pattern of the precordial leads varied little; the amplitude of the individual deflections showed occasional fluctuations, but these were never constant in any one direction. At the age of 2 years left ventricular overactivity was still indicated by large S waves in the right ventricular leads (S V1 25 mm.). By this time right ventricular hypertrophy was also suggested (R V1 20 mm.), and impressive Q waves had developed in standard lead III and unipolar limb lead aVF. These Q waves first appeared when the child was 3 months old and gradually became deeper.

The diagnosis was established when the child was 2 years old by cardiac catheterization, the descending aorta being easily entered through a large patent ductus. There was little change in pressure when the catheter was withdrawn from the aorta to the pulmonary artery and oxygen saturation figures failed to show a left to right shunt at pulmonary artery level when the child

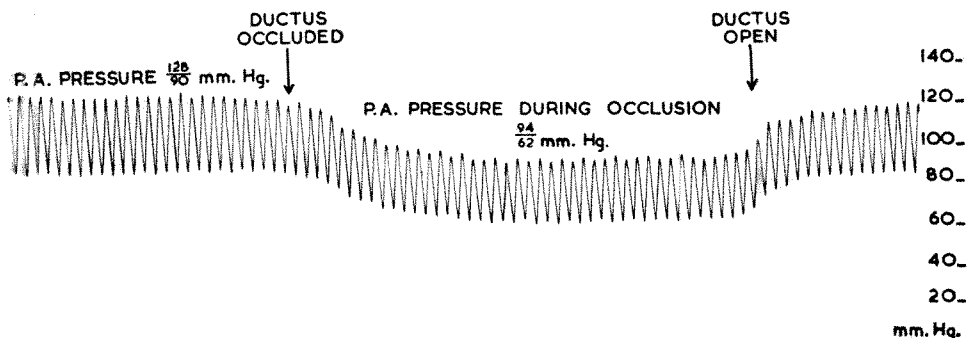


FIG. 2.—Pressure tracing from pulmonary artery at thoracotomy in Case 1, showing fall in pulmonary artery pressure after occlusion of the ductus.

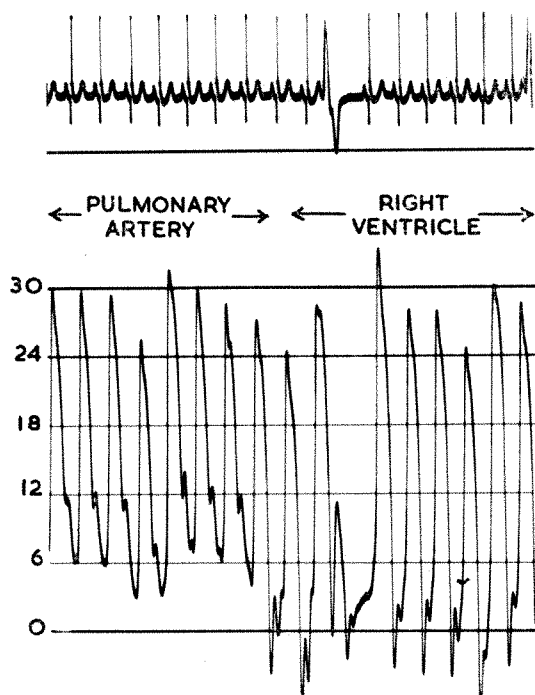


FIG. 3.—Pressure tracing showing normal pressures in pulmonary artery and right ventricle in Case 1, 13 months after operation.

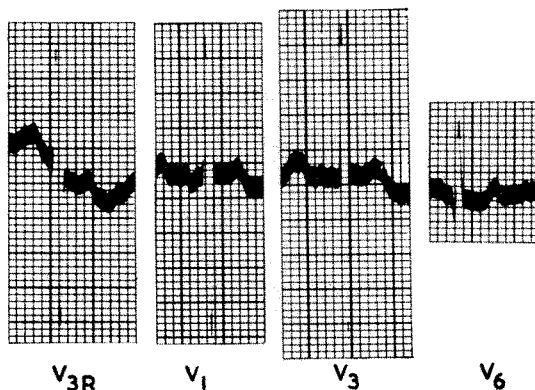


FIG. 4.—Electrocardiogram showing increased R and S waves in V3R and V1 with a normal R wave in V6, a pattern commonly seen in large patent ducts with marked pulmonary hypertension.

was sedated at catheterization (Table 2). Thoracotomy was recommended and a 14-mm. ductus was found. The pressure in the pulmonary artery fell markedly after clamping of the duct (Fig. 2) which was then divided.

The child's general condition rapidly improved following operation and breathlessness became less marked. His subsequent progress has been excellent

with marked increase in activity; he has gained weight more quickly and has been completely free from attacks of bronchitis.

Recatheterization performed 13 months after operation showed a normal right ventricular and pulmonary artery pressure (Fig. 3). Chest radiographs show some pulmonary hyperaemia but the heart size is now normal. The electrocardiogram has also reverted to normal though prominent Q waves persist in leads II, III, and aVF.

COMMENT. This case illustrates how a large patent ductus arteriosus with pulmonary hypertension at systemic level may be mistaken for a more serious lesion. This led to delay in carrying out special investigations which enabled the diagnosis to be made.

Three other infants in this series (Cases 6, 14 and 15) presented similar features and catheterization established the diagnosis in two (Cases 6 and 15, Table 2). All three were dyspnoeic, under weight and suffered from recurrent pulmonary infections. All had 'waterhammer' pulses of a variable degree and two had apical mid-diastolic murmurs. All showed similar electrocardiographic records (Fig. 4), and all had some cardiac enlargement and pulmonary plethora. In these three babies the clinical signs were inconclusive and the results of routine investigations equivocal. It seems that all such obscure cases should be catheterized at an early age if surgical treatment is to be performed while the pulmonary hypertension is still completely reversible.

D.G. Compensatory Patent Ductus Arteriosus. This infant was the first of binovular twins born by breech delivery at full term. She then weighed 4 lb. 12 oz. Late pregnancy had been complicated by moderate toxæmia. There was a history of breathlessness since birth, but cyanosis had not been noticed. Pulmonary infection occurred during the third week of life and cardiac failure developed.

On admission to this clinic at 3 weeks of age the infant was pink and breathless with oedema of feet, arms and eyelids. The arterial pulse was waterhammer in character and a long systolic thrill was present in the pulmonary area. There was a long rattling systolic murmur extending into early diastole in the pulmonary area and an independent mid-diastolic murmur at the apex.

Radiography showed marked cardiac enlargement (C.T. 0.72) and moderate pulmonary hyperaemia (Fig. 5).

Electrocardiography showed right atrial enlargement ($P_2 = 3$ mm. peaked) with low voltage complexes in V3R and V1 and left ventricular hypertrophy with depression of the S-T. segments and inverted T waves in V5 and V6.

Treatment with digoxin and diuretics was followed by some improvement, but feeding remained difficult and she did not gain weight. Heart failure persisted despite treatment. Thoracotomy was therefore recommended when she was 6 weeks of age and a 6 mm. patent ductus was ligated. Following operation the infant's condition deteriorated still further and she died 12 hours later. Autopsy showed tricuspid atresia.

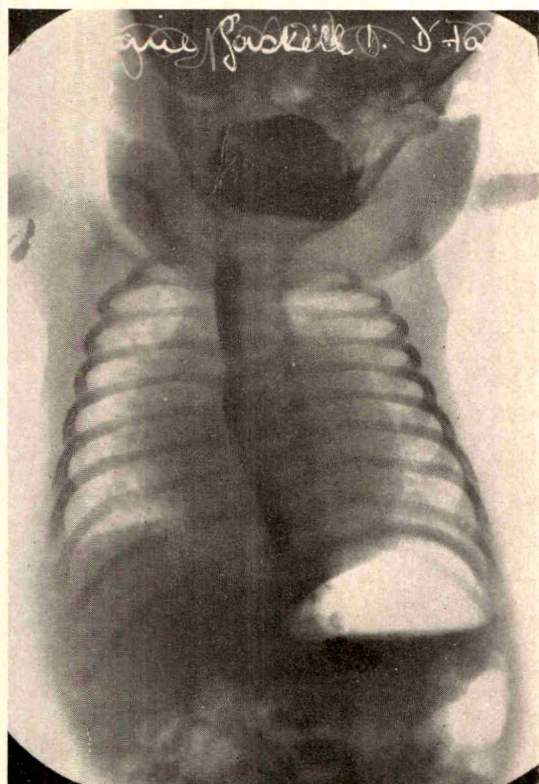


FIG. 5.—Radiograph showing plethoric lung fields in case of tricuspid atresia with overcompensating patent ductus arteriosus.

COMMENT. This case illustrates the extent to which a patent ductus arteriosus may completely dominate the clinical picture even though it is compensating for a lesion which causes pulmonary oligæmia.

Our experience of such dominance is, however, limited to tricuspid atresia, for all our babies with Fallot's tetralogy and pulmonary atresia with a patent ductus, have shown not only central cyanosis, but also normal or diminished pulmonary vascularity.

The fact that heart failure did not respond to medical treatment in this infant and the presence of left ventricular strain in the electrocardiogram should have made the diagnosis of a simple patent ductus arteriosus suspect. In a subsequent similar case attention to these findings enabled us to diagnose the same combination of defects, which were subsequently proved at autopsy.

D.E. Case of Persistent Truncus Arteriosus. This premature infant was born by normal delivery after eight months uncomplicated pregnancy. Initial progress was satisfactory, but increasing breathlessness was noted from the 5th week. On admission to this clinic when 11 weeks old she was pink and moderately dyspnoeic at rest. The waterhammer quality of the arterial pulse was striking. Blood pressure was 120/0 mm. Hg.

A continuous murmur was heard in the pulmonary area and there was an apical mid-diastolic murmur. Phonocardiography confirmed these findings, but the second sound was not seen owing to the high amplitude of the murmur.

Radiologically the heart was enlarged (C.T. ratio 0.75) the oblique views showed selective left ventricular enlargement, and there was increase in the pulmonary vascularity.

The electrocardiogram showed left ventricular hypertrophy with 1 mm. S-T depression and T wave inversion in leads V5 and V6. Right ventricular activity was within normal limits.

The diagnosis of patent ductus arteriosus was made and thoracotomy recommended. At operation, however, a persistent truncus arteriosus was found. The infant's condition deteriorated rapidly during exploration of the chest; ventricular fibrillation developed and she died.

COMMENT. In this case clinical examination suggested a patent ductus arteriosus. The picture was, however, incomplete because splitting of the second sound in the pulmonary area was neither audible nor clearly seen on the phonocardiogram and left ventricular systolic overload in the electrocardiogram was an unusual finding in patent ductus arteriosus in infancy.

This infant is one of a group of 10 cases of persistent truncus arteriosus seen at this clinic. Although cyanosis was prominent in half of these babies the other five were pink when first seen and presented many of the typical features of patent ductus arteriosus. The five acyanotic infants had markedly collapsing pulses and two of them had continuous basal murmurs with independent apical mid-diastolic murmurs. Radiographic and electrocardiographic appearances were similar to those seen in patent ductus arteriosus. These acyanotic infants had severe symptoms and after observation for a few weeks slight cyanosis with feeding became evident and led to further investigation in all except the case described. In two cases, cardiac catheterization demonstrated a left-to-right shunt at pulmonary artery level, but venous angiocardiography failed to reveal the common truncus and patent ductus arteriosus was wrongly diagnosed; both these patients died at thoracotomy. In the other two cases selective angiocardiography with injection of dye into the right ventricle outlined the common trunk and thoracotomy was avoided.

Slight cyanosis after crying or feeding is an extremely important feature in these cases. Angiocardiography is required to make the diagnosis, for cardiac catheterization alone may fail to indicate the ventricular septal defect which is always present with persistent truncus arteriosus, and the increased oxygen level in the blood in the common trunk suggests patent ductus arteriosus. If the right ventricular pressure is at systemic level and the catheter is not passed through a ductus into the descending aorta persistent truncus arteriosus should be suspected and selective angiocardiography should be performed.

Signs of left ventricular systolic overload in the electro-

cardiogram occurred in three cases of truncus arteriosus, but none of the patent ducts, so this should always suggest the possibility of truncus arteriosus. If phonocardiography shows two sounds due to the independent closure of the aortic and pulmonary valves, persistent truncus arteriosus is eliminated.

DISCUSSION

Diagnosis

Clinical Signs. Most authors have emphasized the value of the bounding or brisk peripheral pulses and wide pulse pressure in the diagnosis of patent ductus arteriosus, though varying emphasis is based on their importance. This characteristic pulse persists even during tachycardia or heart failure, as long as the dominant shunt is from aorta to pulmonary artery (Ziegler, 1952). When, however, complete reversal of flow through the ductus occurs the pulses are of normal or small volume (Anderson, Adams and Varco, 1956). Complete reversal of flow is rare in infancy so the waterhammer pulse frequently provides an early clue to diagnosis. It was present in all our cases and we agree with Reinhold (1958) that it is the most important diagnostic sign. There is usually a wide pulse pressure, the aortic diastolic pressure being low; nevertheless, waterhammer pulses were also prominent in those infants with marked pulmonary hypertension; this is probably because the ductus in such cases is a large one and a significant left-to-right shunt still occurs even though the pulmonary artery pressure is very close to the systemic pressure. Indeed, in the presence of marked pulmonary hypertension a waterhammer pulse may be the only clinical sign which suggests a diagnosis of patent ductus arteriosus.

Waterhammer pulses may occur in conditions other than a patent ductus arteriosus, but the most marked examples of such pulsation were observed in acyanotic infants with persistent truncus arteriosus.

The proportion of cases with a continuous murmur varies considerably in published reports of series of patent ductus arteriosus. This may be due in part to the varying number of infants with marked pulmonary hypertension in each series. In addition, the interpretation of the term 'continuous murmur' varies; it is used in this clinic when the murmur continues through the second sound into diastole regardless of its duration in diastole. In our series all cases uncomplicated by marked pulmonary hypertension did have a continuous murmur when first seen, the youngest being 24 days old (Case 2). The typical machinery

qualities of the murmur were uncommon, but a characteristic systolic rattle or crackle as described by Keith, Rowe and Vlad (1958) was often heard.

A mid-diastolic murmur, attributed to increased flow through the normal mitral valve, was a common finding and gave rise to triple rhythm at the apex. Since in some infants this may be the most striking praecordial murmur, even in the presence of marked pulmonary hypertension, its presence should always suggest the possibility of patent ductus arteriosus. An identical murmur, however, may occur in association with ventricular septal defect, persistent truncus arteriosus, aorto-pulmonary window and congenital mitral stenosis.

Of particular interest are the three patients (Cases 1, 6 and 15) in whom the pulmonary artery and aortic pressures were so close. All these patients showed a fall in pulmonary artery pressure when the ductus was clamped at operation and all have done extremely well since operation. In the one which has been recatheterized, the right ventricular and pulmonary artery pressures are normal and there is no evidence of a shunt. This illustrates that despite almost balanced pressures in the pulmonary artery and aorta, the pulmonary artery pressure could revert to normal after treatment and that the factors contributing to the marked hypertension were completely reversible. We do not know when irreversible changes may develop in such a case, but it seems that the earlier the diagnosis is established and treatment carried out the more likely is a complete cure. We stress then the importance of finding a collapsing pulse in an acyanotic patient who may or may not have an apical diastolic murmur, who has plethoric lung fields on the radiograph and electrocardiogram changes described in Case 1. Catheterization should be carried out in the hope of finding a patent ductus arteriosus.

Phonocardiography. Experience with recent cases in this clinic has confirmed the findings of Reinhold and Nadas (1954) in the older child and convinced us of the value of phonocardiography. The graphic record illustrates the onset of the murmur after the first sound and its late systolic accentuation, and confirms its uninterrupted extension into diastole (Fig. 6). Though the loud murmur may mask the second heart sound at the base of the heart, exploration of the whole precordium is worth while as the separate closure of the aortic and pulmonary valves can often be recorded from the lower sternal edge (Fig. 6). The demonstration of these two independent sounds is important in the exclusion of a persistent truncus arteriosus.

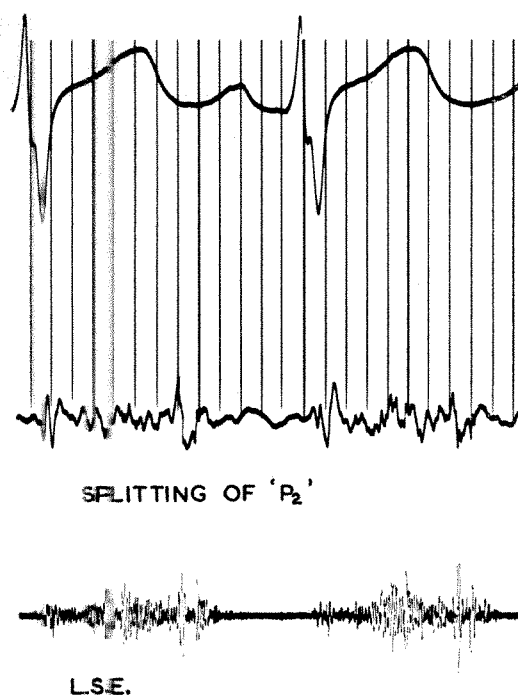


FIG. 6.—Phonocardiogram showing continuous murmur. The two components of the second heart sound were best recorded at the left sternal edge.

Radiography. Some cardiac enlargement and pulmonary plethora is invariable and left ventricular or left atrial enlargement common. The pulmonary arc is often prominent after the early months of life and both this vessel and the aortic knuckle pulsate vigorously on screening. These appearances, though frequent in patent ductus arteriosus, are also found in other lesions, particularly ventricular septal defects.

Electrocardiography. The electrocardiogram may be within normal limits even though the child has symptoms and there is convincing clinical and radiological evidence of a left-to-right shunt (Cases 1, 8 and 22) or marked pulmonary hypertension (Dammann and Sell, 1952). In most cases, however, the electrocardiogram is abnormal. In this series, evidence of isolated left ventricular hypertrophy was the commonest finding. Isoelectric S-T segment and upright T waves of normal or increased amplitude were always present in the left ventricular leads. In contrast, T wave inversion with or without S-T depression appeared in two cases of persistent truncus arteriosus and in both patients in whom tricuspid atresia accompanied patency of the ductus.

Though left ventricular strain may occur in older children with large uncomplicated patent ducts (Cosh, 1957; Hay and Ward, 1956), when it is thought to be due to coronary insufficiency, its presence in infancy makes us suspect some other lesion.

Isolated right ventricular hypertrophy was seen in only one case (Case 19). Clinical examination of this patient did not suggest either the presence of marked pulmonary hypertension or an associated pulmonary stenosis. Unfortunately the child died from fulminating gastroenteritis and autopsy was not allowed. Bauersfeld *et al.* (1957) have, however, reported the presence of isolated right ventricular hypertrophy in patent ductus arteriosus without pulmonary hypertension or pulmonary stenosis being present.

Rudolph *et al.* (1958) stated that combined ventricular hypertrophy frequently occurs in infants with patent ductus arteriosus and this was present in four of our cases (Cases 1, 3, 12 and 15). In these records, left ventricular hypertrophy was diagnosed because of the deep S waves in V3R and V1; the R wave in V6 was not increased in amplitude. The three infants who were proved at cardiac catheterization to have marked pulmonary hypertension showed this pattern on the electrocardiogram and in all three the Q waves were deep in leads I11 and aVF. Unfortunately, all the large ducts have not shown these features and identical records have been found in ventricular septal defects. Nevertheless, when these electrocardiographic changes occur in an infant the possibility of patent ductus arteriosus should be considered.

Deep Q waves are a common feature in infant records in leads I11 and aVF occurring in 40% of normal infants. Nevertheless, deep Q waves occurred in 80% of the infants who had patent ductus arteriosus and their presence may be of help in differential diagnosis as they are in the adult patient with a patent ductus arteriosus accompanied by marked pulmonary hypertension (Wood, 1958).

Right bundle branch block patterns have been reported in infants with patent ductus arteriosus (Ziegler, 1952; Nadas, 1957), but did not occur in our series.

Cardiac Catheterization. This procedure is as safe in infancy as in older patients. Over 50 infants have been catheterized in this clinic without any complication.

Catheterization was done only when the diagnosis could not be established after clinical, radiographic and electrocardiographic examination. In such cases the pulmonary artery pressure is usually at or

near systemic level. The diagnosis of patent ductus arteriosus is often established by passing the catheter through the ductus, which is usually large in such cases, and the presence of a left to right shunt and any right to left shunt can be confirmed by blood oxygen estimations. If, however, the pulmonary artery pressure is at systemic level and the catheter cannot be passed through a ductus or enters a branch of the aorta, usually the right subclavian artery, then further investigation by angiography or aortography is required to differentiate the lesion from patent ductus arteriosus, aortopulmonary window or a high ventricular septal defect in which there was no rise in oxygen saturation at ventricular level.

Angiography. Venous angiocardiology will demonstrate dilution of dye in the pulmonary artery when a patent ductus arteriosus or aortopulmonary window is present if there is a left to right shunt. It may, however, fail to outline a common truncus adequately and has largely been replaced in this unit by selective angiocardiology.

Aortography. Injection into the brachial artery may show a shunt from aorta to pulmonary artery but fail to outline a common truncus. Retrograde aortography when the dye is injected through a catheter with the tip lying above the aortic valves is probably the best way of differentiating the various lesions when the right ventricular pressure is at systemic level. This investigation has a 4% mortality (Bauersfeld *et al.*, 1957) and has not been used in this clinic.

Treatment

It is generally accepted that patent ductus arteriosus should be treated surgically. If symptoms are severe early operation is essential. In the absence of symptoms, Carter and Waterston (1951) advise operation shortly before children start school. We favour earlier surgery when the diagnosis is established in infancy and have advised operation in this age group even though the infants have few symptoms. Spontaneous closure of the ductus is rare, recurrent bronchitis is common, and growth and physical development are often retarded. Infants tolerate operation very well and seem less disturbed by admission to hospital than toddlers and young children.

When the ducts are small they are doubly ligated and in addition transected; when large (over 10 mm.) they are divided.

It is important that operation should not be undertaken during a respiratory infection or in the

presence of heart failure. Even when the ductus is large the patient responds to treatment with digoxin and diuretics, and it is our experience that if congestive cardiac failure persists after medical treatment there is some other lesion present.

SUMMARY

The findings in 28 infants in whom a patent ductus arteriosus was the sole cardiac abnormality are reviewed in an attempt to define the clinical features in infancy and to assess the value of routine radiography and electrocardiography.

The different clinical findings in small and large patent ducts are illustrated and the similarity of this lesion to some cases of persistent truncus arteriosus in the early months of life is described. The pitfalls caused by an overcompensating ductus are discussed.

The indications for cardiac catheterization and angiocardiology and their value in differential diagnosis are also considered. The problems of surgical treatment are mentioned.

We are indebted to Professor J. D. Hay for his advice and criticism of this paper, to Mr. F. R. Edwards and Mr. B. J. Bickford who operated on these cases, and to anaesthetists, Dr. G. J. Rees and Dr. A. Stead. We are also grateful to Dr. Norah Walker and Dr. C. M. Davies for their help in interpretation of the radiographs and angiocardigrams.

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CONGENITAL ADENOMATOID MALFORMATION OF LUNG WITH PNEUMOTHORAX

BY

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Although hamartomas of the lungs are not common, they cannot be considered as pathological curiosities. Several cases have been reported in recent years (Harris and Schattenberg, 1942; Jones, 1949; Thomas, 1949; Timossi, 1955; Lima, Zerbini and Bittencourt, 1955; Gottschalk and Abramson, 1957; Galvez Fermin, 1958; Cornéa, Dichter, Gamentay and Mindru, 1959; Bain, 1959). One variety of hamartoma of the lung, namely congenital cystic disease of the lung, has received an increasing amount of attention since Koontz (1925) collected his large series of cases. Ch'in and Tang (1949) coined the expression 'congenital adenomatoid malformation' for this condition. They found descriptions of 10 cases in the literature up to that time and added one case of their own.

A comprehensive review of the literature was made by Craig, Kirkpatrick and Neuhauser (1956). They mentioned the 11 cases in Ch'in and Tang's paper, 11 other cases and added four of their own. Coffee (1956) also reviewed the position at that time. Since then, one case by Goodyear and Shillitoe (1959) and four cases by Herrmann, Jewett and Galletti (1959) have been reported. These workers distinguished between those cases which present clinically in early neonatal life with cyanosis and those which present later with signs of infection. This report is concerned with a case of congenital cystic disease of the lung which was accompanied by hypoplasia of the entire remaining lung tissue and in which a tension pneumothorax occurred following attempts at resuscitation.

Case Report

Clinical History. The mother was 26 years of age and had had one previous normal pregnancy. Her general health was good. During pregnancy the only abnormality detected was hydramnios at about 27 weeks.

The onset of labour was spontaneous and occurred at the end of the 28th week. The duration of the first

stage was one hour and of the second stage 20 minutes. The presentation was vertex and delivery was spontaneous.

At birth the child was oedematous, cyanosed and apnoeic. Attempts at resuscitation were followed by only two or three shallow gasps.

Radiological Investigation.

ANTENATAL EXAMINATION. The patient was referred for radiological examination (to exclude foetal abnormality or twin pregnancy) on September 22, 1959; the height of the fundus corresponded to that normally expected at 34-35 weeks; by dates, the maturity was 27 weeks. One foetus was present in a vertex L.O.A. position, with evident hydramnios in considerable degree. The foetal stature corresponded to that expected for a maturity of 27-28 weeks. The attitude of the foetus, both of the trunk and the limbs, was reminiscent of that often found in hydrops foetalis and at least suggested the presence of some foetal abdominal distension.

POSTNATAL EXAMINATION. Radiographs (Figs. 1 and 2) were taken of the whole infant shortly after its death which occurred at 10 minutes after birth. It was evident that air had been both swallowed and inhaled. There was slight distension of the abdomen but this was not due to intestinal gas. The thorax presented most unusual appearances. There was a right pneumothorax with a complex loculated appearance peripherally. The margin of this pneumothorax extended well across to the left of the mid-line and no pulmonary aeration was observed on either side. The volume occupied by the left lung was evidently much reduced. The cardiac outline could not be separately discerned. Thus the appearances bore some resemblance to those found in a tension pneumothorax on the right side, but the opacity due to the compressed lung was much greater than would be expected.

Necropsy. This revealed a premature male infant weighing 1,550 g. whose crown-rump length was 28 cm. and crown-heel length was 39 cm. There was marked oedema of the arms and back and the abdomen was distended. There were no other abnormalities seen on external examination. The pleural sacs contained no

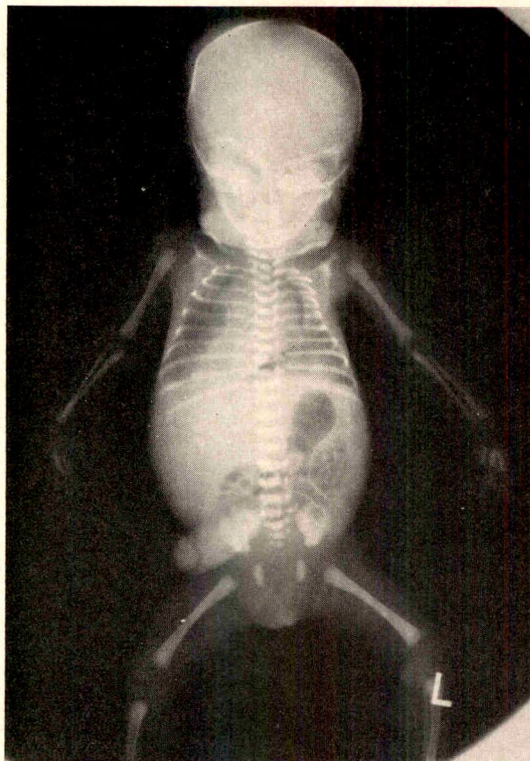


FIG. 1.—Radiograph. Antero-posterior view showing right-sided pneumothorax. There is a cystic space containing air in the mass in the right lung. The mediastinum is displaced to the left.

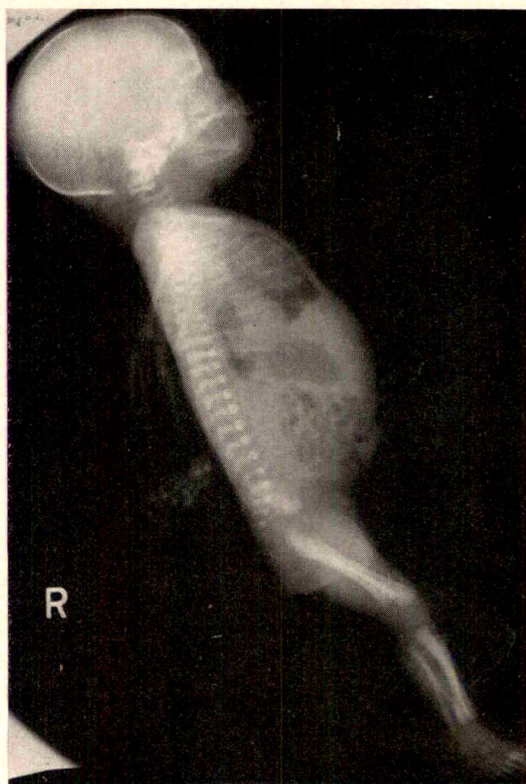


FIG. 2.—Radiograph. Lateral view. Air can be seen in the small intestine.

excess fluid. There was a pneumothorax on the right side which was under tension. The pleurae were glistening. The larynx, trachea and main bronchi were normal. A large, firm, pink, nodular mass involved the upper lobe of the right lung (Fig. 3). On slicing, several cystic cavities were opened (Fig. 4). The mass was approximately three times the usual size of the right upper lobe. A probe could be passed from the right upper lobe bronchus into one of the cysts. The malformation was so large that it had herniated across the midline. The left lung and the middle and lower lobes of the right lung were hypoplastic. The pericardial sac contained no excess fluid. The heart was of the expected size and there were no congenital abnormalities of either the heart or great vessels but the organ was displaced to the left. There was a moderate excess of clear, yellow fluid in the peritoneal sac. The tongue, pharynx, oesophagus, stomach and intestines were normal. The liver was of the expected size and appeared macroscopically normal. The bile passages were patent. The falx cerebri and tentorium cerebelli were intact. There was a small amount of blood diffusely spread in the sub-arachnoid space over both cerebral hemispheres and over the cerebellum. The brain and choroid plexuses were congested. The adrenals (each 1.5 g.), pituitary,

thymus and thyroid glands were normal. The kidneys (each 8 g.) showed foetal lobulation. The ureters, bladder and external genitalia were normal. The placenta weighed 370 g. and measured 17×14 cm. The placental/foetal weight ratio was 1.4:1. There was a velamentous insertion of the cord. The membranes were complete. The placenta was not oedematous and appeared normal on slicing.

Histology.

UPPER LOBE OF RIGHT LUNG. The pleura showed little change. The mass consisted of innumerable small acini lined by a low cuboidal epithelium (Fig. 5). They were separated from one another by a loose connective tissue stroma which contained elastic fibres. Some larger cystic spaces lined by columnar epithelium were also present. These were surrounded by smooth muscle 1-3 layers thick. These structures had the appearance of terminal bronchioles and some showed very marked dilatation (Fig. 6). There was no evidence of cartilage formation in the wall of any of the bronchial-like structures and no glands were present in their sub-mucosa. In a number of areas there were collections of several acini lined by tall, columnar, mucus-secreting epithelium (Fig. 7). The material in the lumen of these



FIG. 3.—Large mass replacing the upper lobes of the right lung. A ruptured cyst is seen in the centre. The left lung is extremely hypoplastic.

structures gave a strongly positive reaction when stained by the periodic acid-schiff technique. The appearance of the mass was consistent with a diagnosis of congenital adenomatoid malformation. There was no subdivision of the mass into lobules. There was a sharp demarcation at the lower border of the mass between malformed tissue and adjoining hypoplastic lung (Fig. 5). A narrow connective tissue septum appeared to separate the one from the other.

MIDDLE AND LOWER LOBE OF RIGHT LUNG. The pleura was healthy. The lobes showed marked hypoplasia and were unexpanded. The bronchi, bronchioles, alveolar ducts and alveoli showed no structural lesion.

LEFT LUNG. This lung was also extremely hypoplastic. The bronchial structure appeared to be normal.

No lesion was found on histological examination of the other organs.

Discussion

Willis (1958) defined hamartomas as tumour-like, but primarily non-neoplastic malformations or



FIG. 4.—Section of the mass showing several large cysts. The middle and lower lobes of the right lung are hypoplastic.

errors of tissue development, characterized by abnormal mixture of tissues indigenous to the part with excess of one or more of these. On these grounds he does not consider 'chondromatous hamartomas' of the lung to be malformations but true tumours. Nevertheless, cartilage-containing

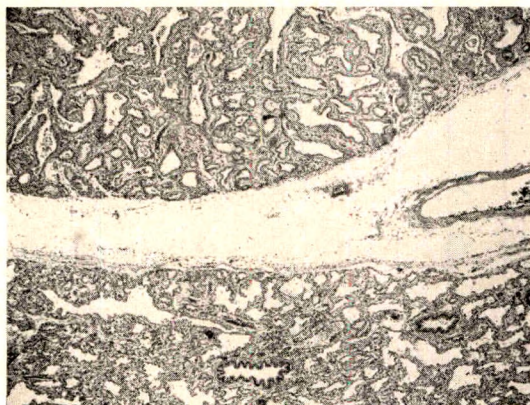


FIG. 5.—Showing adjacent areas of hamartoma (above) and hypoplastic lung. H. and E. $\times 26$.

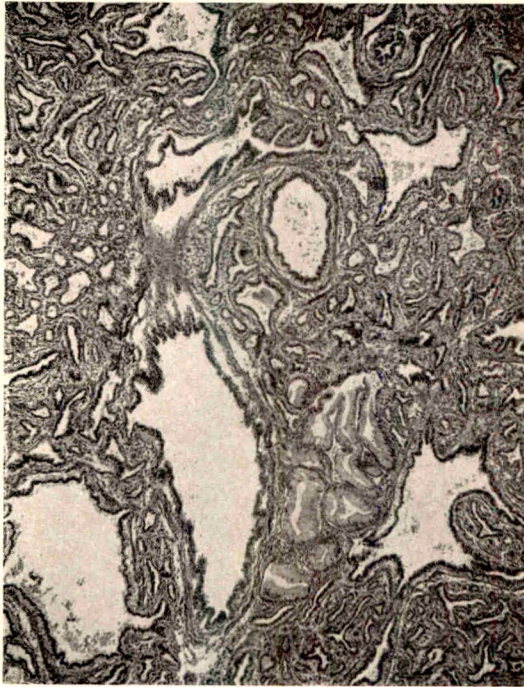


FIG. 6.—Malformation showing large cystic spaces lined by respiratory epithelium and surrounded by some layers of smooth muscle. A focus of mucus-secreting epithelium is present. H. and E. $\times 48$.



FIG. 7.—High power view of part of field in Fig. 3 showing detail of mucus-secreting tissue. H. and E. $\times 103$.

hamartomas are occasionally found in the lungs of infants. Jones (1949) described such a case in which there was an admixture of foetal lung tissue, cartilage and fibrous tissue which had replaced part of one lung of an infant. The appearances were not those of a neoplasm but of a malformation of lung tissue, and the author suggested that this was a true cartilage-containing hamartoma. As well as the more solid type of hamartoma such as described by Harris and Schattenberg (1942), Willis includes congenital cystic disease in this class of disorders of the lungs. Klosk, Bernstein and Parsonnet (1946) define cystic disease of the lung as 'any condition in which the lung parenchyma is replaced by sharply defined cavities containing fluid or air'. These authors divide this disease into the variety which exhibits solitary large cysts and that characterized by multiple cysts. Herrmann *et al.* (1959) describe an acquired type. The cysts in the congenital form of the disease are lined by pseudo-stratified ciliated columnar epithelium or respiratory cuboidal epithelium. In the more common form of cystic disease of the lung, however, cartilage is present in the bronchial wall. It is notably absent in adenomatoid malformation.

Histological examination of the lung in this case showed small cystic spaces lined by a low columnar epithelium of the respiratory variety in most areas. Other parts of the hamartoma contained spaces lined by cuboidal and tall columnar epithelium. Levine (1950) postulates that this form of hamartoma arises by pinching off of portions of the main lung buds and their derivatives in the second half of intrauterine life. Some of these portions of bronchial tissue may completely separate from the bronchial tree and continue to secrete fluid which will distend the cysts. Other portions do not completely separate but maintain a narrow communication with the bronchi. In our case, we were able to pass a probe from a main bronchus into one of the larger cysts. This apparently supports Levine's suggestion as to their mode of origin. Herrmann *et al.* (1959) mention, in addition, a second possible mode of origin, namely a disturbance occurring in the fourth foetal week. At this time two septa divide the foregut into an anterior and posterior part. If cells from this region detach themselves at about this period, then bronchial or gastric cysts would arise. The occurrence of cystic spaces lined by mucus-secreting epithelium

has been noted by previous authors (Ch'in and Tang, 1949; Koboth, 1936) and this suggests that the anomaly may have its origin during the fourth foetal week. Craig *et al.* (1956), however, regard these as aberrant forms of bronchial mucous glands. Conway (1951) believes congenital cystic disease of the lung is the result of some unknown process which interferes with canalization at some point proximal to the termination of the lung bud. Distal to this point canalization begins again producing an isolated canalized segment lined by normal bronchial mucosa. In adenomatoid hyperplasia there is a great increase in the number of structures which have the appearance of terminal bronchioles. The smaller spaces lined by cuboidal epithelium probably represent incompletely formed alveolar ducts.

At necropsy the hamartoma is usually found to increase both the size and weight of the affected lung (the increase in bulk often causing herniation of the lung across the midline with mediastinal displacement) both of which occurred in the present case. In most cases, only one lobe of the lung is affected; indeed, we have found records of only two cases in which an entire lung was involved (Wolman, 1930; Goodyear and Shillitoe, 1959). We have found no preference for the right or left lung and for upper, lower or middle lobes. On slicing the abnormal tissue mass, cysts of varying size are usually seen lying in firm, pale, macroscopically homogeneous tissue. Our case showed relatively few cysts. We found no cartilage in the affected part of the lung and this favours the theory of a valve-like mechanism by which air can enter the spaces of the hamartoma during inspiration but, because of lack of supporting tissue around the communicating channels with the bronchi, air is trapped during expiration. In this way the size of the malformation progressively increases after birth and the 'expanding lung syndrome' is produced. This causes not only displacement of the mediastinum but distortion of the venae cavae and maldevelopment of the contralateral lung. In our case, not only was there hypoplasia of the lung on the opposite side, but of the other lobes of the ipsilateral lung. As in previously reported cases we found no congenital abnormality in any other part of the body.

The diagnosis of this condition is not without difficulty, but, in the present case, foetal abnormality was first considered when hydramnios developed in the 27th week of pregnancy. This is a common feature of cystic disease of the lung, but is unique in that hydrops foetalis was diagnosed by a maternal pelvic radiograph during pregnancy. Ch'in and Tang (1949) and Gottschalk and Abramson (1957)

suggest that the hydramnios is due to cardiovascular disturbance in the foetus following mediastinal and vena caval displacement by the tumour. This is postulated to produce an increase in systemic venous pressure resulting in not only hydrops foetalis but hydramnios. There seems to be little evidence that the oedema is the result of cardiac failure. Generalized anasarca is less common in fetuses with this malformation delivered at term or in infants who live for some time after birth (Craig *et al.*, 1956).

Children suffering from this disease are usually premature; presumably the early labour results from hydramnios. Ch'in and Tang's series consisted mainly of premature and stillborn fetuses, and other cases reported up to 1943 were either stillborn or died in early neonatal life. The mother of our case went into labour at 28 weeks and spontaneously delivered a moderately oedematous and cyanosed infant. Oedema is not unusual in this condition (Grawitz, 1880; Ch'in and Tang, 1949; Craig *et al.*, 1956) and, as mentioned above, is probably due to vena caval distortion. Thus hamartoma of the lung should be borne in mind in the differential diagnosis of cyanosis and oedema in a premature infant.

Tension pneumothorax may result from this malformation (Herrmann *et al.*, 1959), although the vast majority of cases result from rupture of an emphysematous bulla on the surface of the lung or (in slightly older infants) staphylococcal bronchopneumonia. Our case was unusual in that rupture of an air-containing cyst had occurred following attempts at resuscitation.

The cases of Fischer, Tropea and Bailey (1943), of Graham and Singleton (1955), the four cases of Craig *et al.* (1956) and the four cases of Herrmann *et al.* (1959) were all diagnosed during life by radiological examination. This investigation should be performed in all cases in which pulmonary hamartoma is considered as a possible diagnosis.

In retrospect, it seems evident that the loculated appearance in the radiograph of our case was due to air in the superficial cystic parts of the tumour and that a marginal rupture had occurred leading to the pneumothorax. Whilst the limits of part of the tumour were surely outlined, it was not possible to differentiate between the tumour and the atelectatic right lung.

Treatment of this condition is removal of the affected tissue. As the child continues to breathe the cysts in the malformed lung increase in size and progressive displacement of the mediastinum with compression of the contralateral lung occurs. Thus early treatment is imperative, and this, in

turn, depends on early radiological diagnosis of the disease. Our case was complicated by a tension pneumothorax and hypoplasia of all the lung tissue not involved in the hamartoma. The period of survival was insufficient to permit surgical intervention.

Summary

A case of hamartoma of the lung is described in an infant who survived for 10 minutes after delivery. The remaining lung tissue was hypoplastic. A tension pneumothorax was present on the same side as the lesion.

Foetal abnormality was suspected during pregnancy on account of hydramnios. Radiological examination revealed a hydropic foetus. At necropsy a large mass was found replacing the upper lobe of the right lung. On histological examination the mass was found to be composed of multiple small cysts and spaces lined by respiratory type epithelium.

The relationship between congenital cystic disease of the lung and true pulmonary neoplasm is discussed.

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PULMONARY INFECTIONS IN CHILDREN WITH A PARTIAL THORACIC STOMACH ('HIATUS HERNIA')

BY

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During the early stages of a clinical study of the partial thoracic stomach ('hiatus hernia') in children a number of patients were seen who appeared unduly susceptible to pulmonary infections. This observation suggested a possible relationship between the two conditions. The following review was undertaken with the object of either proving or disproving this contention.

Method

The impossibility of obtaining for comparison figures relating to the incidence of pulmonary infections in the childhood population and the lack of objective data upon which to base conclusions presented two major difficulties in carrying out this survey. It was considered that these difficulties could be largely overcome if a suitable sub-division of patients was devised making it possible to compare two groups of children within the series. Such a procedure would dispense with the need of a control group for comparison and, at the same time errors inevitably introduced as a result of varying interpretations of the terms 'bronchitis' and 'pneumonia' would be largely eliminated as these would theoretically occur with equal frequency in either group.

Of necessity, the data for this analysis have been largely derived from the clinical history obtained from parents. A statement to the effect that the child had had either 'bronchitis' or 'pneumonia' as diagnosed by the family doctor has been accepted as a pulmonary infection for the purpose of this survey.

Should there exist a tendency for children with a partial thoracic stomach to develop pulmonary infections it seemed logical to infer that such infection might be related either to the type or frequency of symptoms associated with the patient's gastro-oesophageal abnormality. For this reason the severity of the gastro-oesophageal symptoms has been used as a basis for analysing the data relating to these patients. The following two symptom

groups have been defined based on a previous classification (Carré, 1959):

Group X: Vomiting and/or difficulty in swallowing solid food occurring on average more frequently than once a month.

Group Y: Vomiting and/or difficulty in swallowing solid food occurring on average less often than once a month.

Such a classification, however, does not provide for a clearcut sub-division of patients because of the symptomatic improvement shown by the majority with advancing age (Carré, 1959). It is apparent that at a particular age a child's symptoms might conform to Group X severity but a year later be those of Group Y. To overcome this difficulty each patient has been classified as having symptoms of either Group X or Y severity for each year of age. For example, a child who suffered from frequent symptoms for more than six months of the age period 1-2 years would be classified under Group X for that period, and similarly would be reclassified under Group Y for the age period 2-3 years if symptoms had subsided to conform with this grouping.

In this way two series of 12 monthly age periods have been obtained. On the one hand a series consisting of annual periods during the major portion of which symptoms of Group X severity were recorded and on the other hand a series of annual periods during which less troublesome symptoms were noted (Group Y). In addition, the occurrence of pulmonary infections, night vomiting and dysphagia with solid food have been recorded in respect of each annual age period.

Selection of Patients

Children considered in this survey all had a small portion of stomach protruding into the chest through the oesophageal hiatus. The gastro-oesophageal junction was in every instance situated along the upper border of the intra-thoracic gastric

TABLE 1
ASSOCIATION OF PULMONARY INFECTION WITH FREQUENCY AND TYPE OF VOMITING

Age Period (years)	Clinical Group	No. of 12-monthly Age Periods	No. of 12-monthly Periods During which Following Symptoms were Noted				
			Pulmonary Infection	Dysphagia	Dysphagia and Pulmonary Infection	Night Vomiting	Night Vomiting and Pulmonary Infection
1-2	X	37	15	13	2	30	15
	Y	41	2	2	0	3	0
2-3	X	22	6	7	1	14	5
	Y	52	8	2	1	5	1
3-4	X	19	5	12	4	13	4
	Y	30	4	2	0	2	0
4-5	X	9	0	5	0	4	0
	Y	18	2	1	0	4	1
1-5	X	87	26	37	7	61	24
	Y	141	16	7	1	14	2

Group X Attacks of vomiting and/or dysphagia occurring more frequently than once a month during at least six months of any one year of age.

Group Y Fewer symptoms than Group X.

loculus. Surgically treated patients have been excluded.

As it was intended to compare the occurrence of pulmonary infections with specific clinical disturbances, such as night vomiting and difficulty in swallowing solid food, the age period reviewed has been restricted to over 1 year, when both these features could be more accurately determined. With relatively few children over 5 years available for study this age has been adopted as the upper limit for consideration.

Except where specifically stated the following analysis is restricted to patients who had no associated oesophageal stricture. Information relating to 78 patients has provided 228 annual periods for analysis.

Results

A pulmonary infection was recorded for 26 of the 87 annual age periods (29.9%) during which symptoms were classified as of Group X severity and for 16 of 141 periods (11.3%) during which symptoms were minimal, Group Y (Table 1). This difference in incidence is statistically significant ($p < 0.001$).^{*} These observations confirm that pulmonary infections are commoner in children with a partial thoracic stomach during periods when vomiting is frequent.

In theory this significantly higher recorded incidence of pulmonary infections during Group X annual periods could be related not to the frequency of symptoms but to the occurrence either of dysphagia with solid food or night vomiting, both of which were frequently noted clinical features during these periods. To test this hypothesis a further analysis of Group X periods has been undertaken as follows.

Difficulty in swallowing solid food was a recorded symptom during 37 of the 87 Group X annual periods; a pulmonary infection was recorded during seven of these 37 periods (18.9%). The comparable figures for periods during which dysphagia was not a complaint were 19 of 50 (38%). However, when annual periods were excluded during which night vomiting was also a feature these figures become two of 19 (10.5%) and none of seven respectively. Information relating to patients with an associated oesophageal stricture has been analysed in a similar manner. In all these children the predominant and often only symptom was difficulty in swallowing solid food. In only four of 37 annual periods was a pulmonary infection noted, an incidence of 10.8%. Allowing for the small figures involved, these latter estimates (10.5, 0 and 10.8%) conform with the observed frequency of pulmonary infections during the Group Y periods (11.3%) when clinical disturbances were judged to be infrequent. The occurrence of dysphagia therefore appears to have no direct bearing on the increased incidence of pulmonary infections noted during periods of frequent symptoms.

On the other hand, a pulmonary infection was recorded during 24 of 61 annual Group X periods (39.3%) during which night vomiting was a feature. The comparable figures for Group X periods during which night vomiting was not a complaint were two of 26 (7.7%). This difference is statistically significant ($0.01 > p > 0.001$). Furthermore, the frequency of pulmonary infections during Group X periods when night vomiting was not recorded (7.7%) is similar to that estimated for Group Y (11.3%).

Radiological Observations

Segmental pulmonary lesions have been identified radiologically on 19 occasions in 17 of 242 children with a partial thoracic stomach (Table 2). These lesions were confined to the right lung in 13 and the left in four; in two instances both lungs were involved. A single lobe was involved in 16 instances. In 10 of the 12 right-sided lesions the affected area was either the middle or upper lobe. Of the four left-sided lesions the upper lobe was the affected site in two.

At the time of demonstrating these lesions eight patients were aged less than 12 months, seven were between 1 and 3 years old and four were more than 3 years of age.

TABLE 2
RADIOLOGICALLY CONFIRMED PULMONARY LESIONS

Patient	Lobe of Lung Affected (Collapse/Consolidation)	Age (yrs) (mths)	
T.B.	R.U.		10
A.S.	R.M.	7	2
E.W.	L.U.	1	3
D.Ru.	R.L.		11
	L.U.	1	9
R.Ha.	R.M.		2
R.Gi.	R.M. and L.U.	1	1
	R.M.	1	4
M.W.	L.L.	4	6
W.J.	R.M.	1	2
C.N.	R.M.		3
S.G.	R.M.		2
A.S.	R.U.		7
P.W.	R.U.		2
M.L.	L.U. and R.M.	3	1
J.D.	R.L. and R.M.	7	0
J.M.	L.L.		8
D.H.	R.M.	2	5
S.S.	R.L.	2	9

Lobe affected: R.U. = right upper R.M. = right middle
R.L. = right lower
L.U. = left upper L.L. = left lower

* In all quoted statistical analyses $p < 0.05$ has been accepted as evidence of significance.

Discussion

It has been shown that in children with a partial thoracic stomach the risk of acquiring a pulmonary infection is greatly increased if vomiting at night is a symptom. In the present study the occurrence of night vomiting was associated with more than a threefold increase in the number of recorded pulmonary infections. On the other hand no relationship could be demonstrated between the development of pulmonary infections and either frequent day vomiting or dysphagia with solid food.

These findings suggest that many of the pulmonary infections recorded in children with a partial thoracic stomach result from the inhalation of vomited material at a time when the patient is in a semi-conscious state. The radiological observa-

tions recorded in this study are interpreted as supporting such a contention. These show a preponderance of single lobe lesions with the right lung principally affected, a distribution demonstrated by Brock, Hodgkiss and Jones (1942) as characteristic of the inhalation of foreign material during recumbency. However, an unusually large number of right middle lobe lesions were noted in the present series. This may be due to the fact that while still only half awake many patients will sit up and lean forward when vomiting thereby assuming a posture suited to the inhalation of material into the right middle lobe bronchus (Foster-Carter, 1943).

Radiographically defined pulmonary lesions were most frequently noted in patients under 3 years of age. In view of the association between night vomiting and pulmonary infections these findings are to be expected as most children with a partial thoracic stomach suffer from progressively fewer gastro-oesophageal symptoms (including night vomiting) as they grow older (Carré, 1959).

Summary

A study is described in which the occurrence of pulmonary infections in children with a partial thoracic stomach has been related to specific symptoms referable to the patient's gastro-oesophageal abnormality. The results indicate that the incidence of pulmonary infections in children with a partial thoracic stomach is considerably increased if night vomiting is a symptom. On the other hand there is no reason to believe that frequent day vomiting or difficulty in swallowing solid food predispose to the development of pulmonary infections.

Evidence is quoted in support of the view that many of the pulmonary infections noted in patients with night vomiting result from the inhalation of vomited material.

I am greatly indebted to Dr. R. Astley of the Children's Hospital, Birmingham, and Dr. F. Plarre of the Royal Children's Hospital, Melbourne, Australia, for the radiological assessment of the patients considered in this study. I wish to thank also the consultant physicians and surgeons of the Children's Hospital, Birmingham, the Royal Children's Hospital, Melbourne, and the Royal Belfast Hospital for Sick Children for permission to review their patients and Mr. J. D. Merrett of Queen's University, Belfast, for help with the statistical analysis.

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THE FATE OF THE PARTIAL THORACIC STOMACH ('HIATUS HERNIA') IN CHILDREN

BY

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In a previous communication it was estimated that about two of every three clinically affected infants with a partial thoracic stomach cease vomiting spontaneously before 2 years of age in the absence of either postural or surgical therapy (Carré, 1959). What then happens to the gastro-oesophageal abnormality in such children? Does the partial thoracic stomach undergo anatomical restitution?

Evidence has been presented elsewhere confirming the value of adequate postural therapy in the management of infants with a partial thoracic stomach (Carré, 1957). What, however, is the effect of such treatment on the radiological 'cure' rate? The present review is aimed at answering these questions.

Observations

Three studies are included and each is considered separately.

1. A retrospective reassessment of patients given neither postural nor surgical treatment.
2. A prospective follow-up of similarly untreated patients.
3. A prospective follow-up of clinically affected infants treated by adequate sustained posture.

All children considered in this survey had a small loculus of stomach protruding through the oesophageal hiatus into the chest. The gastro-oesophageal junction was situated in every instance along the upper border of the intrathoracic portion of stomach. Children with gastro-oesophageal incompetence but no definite intrathoracic gastric loculus (i.e. 'chalasia') have not been included.

Retrospective Review of Untreated Patients. The following review is based on a study undertaken at the Children's Hospital, Birmingham, during 1951-53. There seemed then no reason to suppose that the increase in the number of children recognized as having a partial thoracic stomach reflected

anything more than improved diagnosis and a greater awareness of the condition. This being so, it was argued that provided the abnormality persisted, even despite cessation of symptoms, it should be possible to recognize such cases in retrospect. The following retrospective follow-up study was therefore undertaken.

Hospital case records relating to patients admitted to the Children's Hospital, Birmingham, during the 10 years, 1941-50 inclusive, because of either vomiting of uncertain cause or vomiting ascribed to feeding difficulties, pylorospasm, 'habit' or 'cyclical' vomiting and peptic ulceration were examined. Patients whose listed clinical features and progress appeared similar to those of children with a proven partial thoracic stomach were selected for review. In addition, all patients admitted to hospital during the 20-year period 1930-50 and diagnosed as having a lower oesophageal abnormality were included for clinical and radiological reassessment.

One hundred and forty-seven patients were selected for review. Three children were unable to attend for examination, six others had died and 21 (14.3%) remained untraced. All 117 children who attended were examined by one of us (I.J.C.) and the clinical history re-evaluated. These children were then examined radiologically. At the time of examination the radiologist (R.A.) was kept in ignorance of the clinical history obtained. He was aware, however, that all children being examined as part of this investigation had previously attended hospital because of vomiting.

At the time of their reassessment patients were divided into two groups. One consisted of children whose clinical progress appeared on re-evaluation to have conformed with the general pattern observed in children with a proven partial thoracic stomach; children in this group were considered on clinical grounds as likely to show abnormal radiological findings. Children in the second group were

assessed as having atypical clinical histories and therefore unlikely to show any gastro-oesophageal abnormality on radiological examination. Subsequent comparison of the radiological and clinical findings showed a high degree of correlation. A partial thoracic stomach was demonstrated radiologically at the first examination in 35 of the 52 children selected on clinical grounds as likely to have this abnormality. In an additional eight, free gastro-oesophageal reflux was demonstrated but no intrathoracic loculus of stomach could be defined with certainty. The radiological appearances in the other nine children appeared 'normal'. In only four of 65 children in the second group was a partial thoracic stomach demonstrated. Sixty-one were classified as showing no radiological abnormality.

In view of extremely suggestive clinical histories, 12 of the 17 children in whom a definite partial thoracic stomach could not be defined, were re-examined radiologically. On this second occasion a small partial thoracic stomach was demonstrated on fluoroscopy in two children previously noted as having free gastro-oesophageal reflux only and in one of those considered 'normal'. The results of these observations are shown in the Table.

TABLE
RETROSPECTIVE FOLLOW-UP REVIEW

Likelihood of Partial Thoracic Stomach from Clinical Assessment	Number of Patients	Radiological Findings		
		Positive	Doubtful (Gastro-oesophageal Reflux only)	Considered 'Normal'
Probable	52	38	6	8
Unlikely	65	4	0	61
	117			

Of 52 patients whose early progress was considered typical of that of children with a partial thoracic stomach, 44 were free of troublesome symptoms when seen, i.e. vomiting and/or dysphagia occurred less than once a month. A partial thoracic stomach was demonstrated radiologically in 30 of these 44 patients; 10 of these had been virtually free of symptoms from infancy. These patients had first attended hospital some two to 18 years previously.

Prospective Follow-up of Untreated Patients. Almost every child with a partial thoracic stomach seen since 1951 has been treated by either posture or surgery. For this reason, few patients are suitable for consideration. Only untreated patients

in whom a partial thoracic stomach was recognized before 2 years of age have been considered. Of these, 10 have been re-examined by barium swallow and fluoroscopy at least two years after cessation of symptoms. A partial thoracic stomach was still demonstrable in eight. In five patients the follow-up was of five years or more; a definite partial thoracic stomach was seen in three.

Prospective Follow-up of Clinically Affected Infants treated by Adequate Sustained Posture.

Twenty patients who were first started on adequate sustained postural treatment before 3 months of age were free of symptoms at the time of their last examination by barium swallow and fluoroscopy. All these patients had been maintained in a sitting posture throughout the 24 hours for at least six months. At the time of their examination these children had been free of symptoms for periods varying from two to seven and a half years. An intrathoracic gastric loculus was still demonstrable in 13. Ten children had been free of symptoms for more than five years; a partial thoracic stomach was defined in seven of these.

Discussion

During the 'retrospective' follow-up investigation of patients with a partial thoracic stomach the opportunity was taken to record independent clinical and radiological observations. A very high degree of correlation was obtained, thereby further confirming the specific nature of the clinical disturbances.

The investigation included the examination of 44 virtually symptom-free persons who had suffered from symptoms during infancy and early childhood comparable to those experienced by patients with a partial thoracic stomach. In 17 no gastro-oesophageal abnormality was demonstrated on the first fluoroscopic examination. Nonetheless, the early clinical progress of these 17 patients had been so similar to that of patients with a partial thoracic stomach that it was our belief that they too had had an identical gastro-oesophageal abnormality. The demonstration of a partial thoracic stomach in three of 12 individuals who were re-examined tends to confirm such an assumption. If it is accepted that the clinical disturbances suffered by all 44 patients during their infancy and early childhood were related to the presence of a partial thoracic stomach, then the incidence of spontaneous radiological 'cure' (i.e. failure to demonstrate a gastro-oesophageal abnormality) among these individuals may be assessed as about one in three (14 of 44). Confirmation of these deductions is provided by the

'prospective' follow-up review of untreated patients in which a similar radiological 'cure' rate was obtained.

The radiological 'cure' rate of one in three (seven of 20) among infants treated conservatively is comparable to that computed for untreated patients. There is therefore no evidence from this study that postural treatment results in an increased incidence of radiological 'cure'.

The observations recorded in this review further confirm our previously expressed opinion that despite cessation of symptoms a partial thoracic stomach will remain fluoroscopically demonstrable during childhood in the majority of instances (Carré, Astley and Smellie, 1952). More recently Swyer (1955), Guichard, Verger and Humeau (1956), Masse and Bader (1957) and Burke (1959) have reported similar observations.

Evidence has been quoted both in this and in a previous communication (Astley and Carré, 1954) showing that a negative radiological examination does not necessarily exclude a partial thoracic stomach. Plarre (1956) has also stressed this fact.

Thus, the negative radiological findings recorded in about a third of our symptomless patients should not be interpreted as proof of anatomical cure.

We are grateful to the consultant physicians and surgeons of the Children's Hospital, Birmingham, for permission to examine and follow-up their patients.

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THE BACTERIAL FLORA OF THE STOMACH AND SMALL INTESTINE IN CHILDREN WITH INTESTINAL OBSTRUCTION

BY

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The alimentary tract at birth is either sterile or contains only a few micro-organisms (Wilson and Miles, 1955). Within a few days of birth a profuse flora is established in the mouth and large intestine. However, the small intestine remains relatively free from micro-organisms throughout life (Cregan and Hayward, 1953; Anderson and Langford, 1958a). Thus in health it seems that some antibacterial mechanism is present which prevents a resident flora from becoming established in the small intestine.

The nature of this antibacterial mechanism is obscure. Cregan, Dunlop and Hayward (1953) have shown it to be independent of the gastric germicidal barrier. Anderson and Langford (1958a) have previously suggested that maintenance of normal intestinal motility is important. Evidence for this suggestion has been sought in the present study, which is an investigation of the flora of the small intestine in conditions where intestinal motility is affected by obstruction to the onward passage of intestinal contents. The patients examined included newborn and older children with obstructive lesions of differing aetiology and duration at differing sites along the small intestine.

A search of the literature did not reveal any previous investigation in newborn or older children or even any thorough investigation of the intestinal flora in adults with intestinal obstruction. Therefore this paper will also describe the extent and nature of the flora of the small intestine in children with intestinal obstruction. The results of a similar study in adults are reported elsewhere (Bishop and Allcock, 1960).

Material and Methods

Clinical Material. Twelve newborn babies aged from 1 to 7 days, in whom obstruction had been present at birth, were examined. These patients included one with volvulus of the stomach, two with duodenal atresia, three

with jejunal atresia, one with Hirschsprung's disease and five with meconium ileus.

In addition 12 children aged from 10 days to 13 years in whom obstruction had developed acutely and one child of 17 months with subacute obstructive symptoms since birth were examined. The pathological conditions responsible for the obstruction and the duration of obstruction before operation were extremely varied and are recorded in Table 1.

Clinical findings relevant to the investigation were recorded for each patient on a specially compiled proforma. The data sought included duration and character of any vomiting, time of the last bowel action, details of any preoperative antibiotics and a description of the findings at operation.

Collection of Specimens. Specimens of intestinal contents were obtained in the following order from patients during operation for relief of the obstruction: from stomach via Ryle's tube; swab of free fluid in the peritoneal cavity; from small intestine approximately 10 cm. distal to obstruction; from small intestine approximately 10 cm. proximal to obstruction; from other levels of small intestine proximal to the obstruction, depending on the level of obstruction.

The contents of the small intestine were sampled using the following direct needling technique originally described by Cregan and Hayward (1953). At operation 2 ml. of sterile Ringer's solution were injected into the lumen of the bowel which was washed with this fluid by gently sucking back and forth with the syringe. The resultant diluted intestinal contents were then withdrawn. In order to keep the technique of sampling uniform, this procedure was always used even when the obstructed intestine contained sufficient fluid for direct aspiration.

Bacteriological Examinations. Usually within three hours of collection two drops (about 0.06 ml.) of each specimen were inoculated on to each of the following media: horse blood agar and plain desoxycholate agar incubated aerobically at 37° C.; horse blood agar incubated anaerobically at 37° C. with 5-10% added CO₂. The range of media and conditions of incubation

TABLE 1
BACTERIAL FLORA IN INTESTINAL OBSTRUCTION IN BABIES AND OLDER CHILDREN

Case No.	Age	Cause of Obstruction	Duration of Obstruction (days)	Stomach	Duodenum		Jejunum		Ileum		Colon
					Above	Below	Above	Below	Above	Below	
1	6 days	Volvulus of stomach	6	±O ±F	±O	■					
2	4 days	Duodenal atresia	4	±O	±O	■					
3	5 days	Duodenal atresia	5	±O	±O	■					
4	17 mths	Duodenal stenosis	(17 mths subacute)	■	■	nt					
5	7 wks	Adhesions following Ramstedt's operation	8 hours	±O ±F	nt		±F	nt			
6	1½ days	Jejunal atresia	1½	+++F	nt		+++F	■			
7	4 days	Jejunal atresia	4	+++F	nt		+++F	■			
8	5 days	Jejunal atresia	5	+++F	nt		+++F	■			
9	10 days	Universal mesentery with volvulus	12 hours	nt	nt		++F		+++F	nt	
10	13 yrs	Adhesion	1	±O	nt		nt		+++F	nt	
11	4 wks	Band obstruction from Meckel's diverticulum	1	nt	nt		nt		++F	++F	
12	3 mths	Inflammation of Meckel's diverticulum with stenosis of ileum	1½	■	nt		nt		+++F	++F	
13	2 days	Meconium ileus	2	■	nt		■		■	nt	
14	2 days	Meconium ileus	2	nt	nt		■		++F	■	
15	7 wks	Intrauterine perforation and peritonitis, subsequent stenosis of ileum	2	+++F	nt		+++F		+++F	■	
16	6 yrs	Appendicular abscess	3	nt	nt		+++F		+++F	++F	
17	3½ days	Meconium ileus	3½	+++O +++F	nt		+++O +++F		+++O +++F	nt	
18	3½ days	Meconium ileus	3½	±O	nt		+++F		nt	■	
19	3 mths	Postoperative adhesions	4	++F	nt		nt		+++F	■	
20	8 yrs	Adhesions from appendicitis	5	nt	nt		nt		+++F	■	
21	7 days	Meconium ileus	7	nt	nt		+++F		±F	nt	■
22	3 yrs	Intussusception	18 hours	nt	nt		nt		+++F		
23	13 yrs	Caeco-colic intussusception	18 hours	nt	nt		nt		±O +++F		
24	6 mths	Caeco-colic intussusception	1	nt	nt		nt		++F		
25	4 days	Hirschsprung's disease	4	±O	nt		+++F		+++O +++F		

The vertical line in heavy type denotes level of obstruction.

O denotes a flora of oral type.

F denotes a flora of faecal type.

Plusses indicate degree of growth: ± and + denote transient flora; ++ and +++ denote resident flora (see text).

nt denotes not tested.

■ denotes sterile.

were chosen so that the growth requirements of all bacteria likely to occur in the intestinal tract would be satisfied. Direct smears were always examined as a check on the adequacy of conditions of culture. A standard plating technique was used (Cregan and Hayward, 1953) and the degree of growth was graded from ± to +++. A scanty growth (± or +) was regarded as a transient flora unable to multiply at the site sampled. A profuse growth (++ or +++) was regarded as a resident flora. As well as the plating technique, the criteria for interpretation of quantitative results described fully by Cregan and Hayward (1953) were followed exactly.

Results

Table 1 shows quantitative results from the 25 patients examined. Table 2 shows qualitative results from the 19 children with an abnormal profuse flora (++ or +++) in the small intestine. In both Tables the results from newborn and older children have been combined since no bacterio-

logical difference between these two groups was observed.

Specimens Proximal to the Point of Obstruction.

Quantitative and qualitative results from specimens proximal to the point of obstruction differed with the level of obstruction. All specimens from four children with obstruction proximal to the duodeno-jejunal flexure (Cases 1-4) were either sterile or contained only a scanty flora usually of oral type. By contrast in almost all (19 out of 21) children with obstruction distal to the duodenal-jejunal flexure (Cases 5-25) a profuse flora of faecal type was present in the small intestine above the point of obstruction. Stomach specimens from 12 of these children were also examined. Six yielded a profuse faecal flora and six were either sterile or yielded only a scanty flora of oral type.

Since 12 children received antibiotics parenterally before operation it was important to be sure that

TABLE 2
BACTERIAL FLORA OF THE SMALL INTESTINE
IN ACUTE INTESTINAL OBSTRUCTION

Faecal Type Organisms	No. of Times Isolated	Oral Type Organisms	No. of Times Isolated
<i>Bact. coli</i> type I	15	<i>Staph. saprophyticus</i>	4
<i>Cl. welchii</i>	9	<i>Staph. afermentans</i>	2
<i>Strep. faecalis</i>	7	<i>Staph. lactis</i>	2
<i>Bacteroides</i> sp.	6	<i>Staph. aureus</i>	2
<i>Paracolon</i> sp.	5	<i>H. parainfluenzae</i>	2
<i>Veillonella gazogenes</i>	4	<i>Strep. agalactiae</i>	2
<i>Bact. aerogenes</i> type I	3	<i>Strep. mitis</i>	5
<i>Bact. coli</i> irregular type	2	<i>Strep. S.B.E.</i>	1
<i>Bact. coli</i> intermediate type I	2	<i>C. xerosis</i>	1
<i>Strep. ligesfaciens</i>	2		
<i>Strep. zymogenes</i>	2		
<i>Cl. fallax</i>	1		
<i>Cl. paraputrificum</i>	1		
<i>Cl. multifermentans</i>	1		
<i>Pr. mirabilis</i>	1		
<i>Pr. vulgaris</i>	1		
<i>Veillonella parvula</i>	1		
<i>Achromobacter</i> sp.	1		
<i>Alcaligenes faecalis</i>	1		
<i>Candida albicans</i>	1		

Number of cases with abnormal resident flora = 19.

this had no effect on the bacteriological results. The antibiotics used were tetracycline or penicillin and streptomycin given intramuscularly or intravenously as one dose (Cases 6, 7, 11, 13, 14, 15 and 17) or as a more prolonged course (Cases 2, 8, 10, 16 and 19). The small intestine of five of the former and four of the latter contained a profuse faecal flora at operation, so that it is unlikely that the results from the remaining three, that yielded only scanty flora, could be attributed to suppression of bacterial growth in the bowel lumen by the pre-operative parenteral antibiotics.

Specimens Distal to the Point of Obstruction.

Unlike the proximal specimens, results from specimens distal to the point of obstruction were quantitatively and qualitatively independent of level of obstruction. Of 14 samples from below the obstruction, 11 were sterile. The remaining three (Cases 11, 12 and 16) yielded a profuse faecal flora but the intestinal lumen of each of these three children was only partially obstructed and it was concluded that the results were invalid due to contamination with fluid from above the point of obstruction.

Peritoneal Swabs. These specimens were obtained from eight children and were always sterile when the bowel was viable. In three children there was a portion of non-viable bowel (Cases 9, 11 and 16). In one of these (Case 9) the peritoneal swab was sterile. In the other two a faecal flora was isolated and was found to be qualitatively similar to that present in the intestinal lumen.

Qualitative Results. Table 2 shows that organisms of faecal type were common in the small intestine of the 19 patients yielding abnormal quantitative (++ or +++) results. Oral type organisms were only occasionally isolated. *Bact. coli* type I was present in 15 of the 19 children. *Cl. welchii* was present in less than half of the cases examined, an incidence much less than that found in a similar study in adults (Bishop and Allcock, 1960). None of the faecal type organisms were outside the range of those likely to occur in the healthy large intestine.

Discussion

A search of the literature of the past 60 years has not revealed any detailed investigation of the bacterial flora of the small intestine in intestinal obstruction either in children or in adults. Williams (1926, 1927) examined vomitus and small intestinal contents from adults with intestinal obstruction. However, his samples of small intestinal contents were restricted to the point of intestinal resection and the bacteriological techniques were directed mainly towards isolation of *Cl. welchii*. In the present investigation the technique of sampling allowed several levels of intestine to be examined even when no intestine was resected and the bacteriological techniques used were directed at isolating and fully identifying all species of bacteria present.

No difference was found between the results from babies and those from older children. The overall results from all children are therefore presented diagrammatically in Figs. 1 and 2. When obstruction was present proximal to the duodeno-jejunal flexure (Fig. 1) the small intestine and stomach remained bacteriologically normal, i.e. were either sterile or contained only a scanty flora. When obstruction was present distal to the duodeno-jejunal flexure a profuse faecal flora was found above the point of obstruction (Fig. 2). Regardless of the level of obstruction, small intestine distal to the point of complete obstruction remained bacteriologically

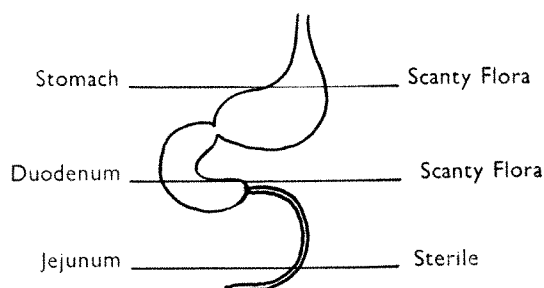


FIG. 1.—Extent of flora in gastro-intestinal tract when obstruction was in the region of duodeno-jejunal flexure.

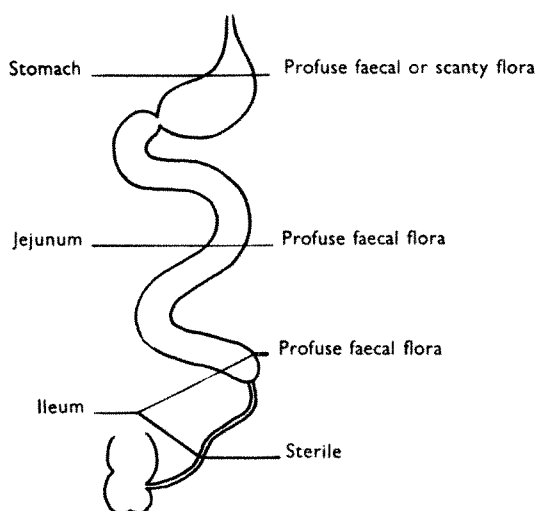


Fig. 2.—Extent of flora in gastro-intestinal tract when obstruction distal to duodeno-jejunal flexure.

normal. This was not necessarily so when obstruction was incomplete. These results indicate that the profuse faecal flora present in the small intestine above an obstruction is derived by ingestion and not by retrograde spread from the colon. This is confirmed by the results of Bishop and Allcock (1960) in adult patients.

Since the profuse faecal flora present in the small intestine above an obstruction is derived by ingestion, it follows that even in health faecal organisms frequently escape the gastric germicidal barrier and contaminate the small intestine. However, faecal organisms do not proliferate in the healthy small intestine since it has been shown to contain only a scanty flora usually of oral type (Cregan and Hayward, 1953; Cook, Elliott, Elliot-Smith, Frisby and Gardner, 1957; Anderson and Langford, 1958a). It is surprising that these organisms do not proliferate in the healthy small intestine since conditions of pH, of temperature and oxygen tension are favourable to their growth. Thus in health some mechanism must prevent the growth of a profuse flora in the small intestine.

The nature of this mechanism is not well understood. It has been shown to be independent of the gastric germicidal barrier (Cregan *et al.*, 1953) and therefore must depend on other factors, perhaps either chemical or mechanical, present in the small intestine. It is possible that the small intestine secretes a chemical which is either bacteriostatic or bactericidal. However, the absence of pancreatic secretion (Anderson and Langford, 1958a), or of bile (Anderson and Langford, 1958b) does not

affect the flora of the small intestine and no other secretion with antibacterial activity against the species of micro-organisms isolated in this study has yet been demonstrated. If a chemical antibacterial substance exists in the small intestine it must be neutralized in some way in the terminal ileum or colon. Alternatively, it is possible that the antibacterial mechanism is dependent on mechanical factors such as constant secretion and movement of intestinal contents which might wash through all contaminating bacteria at a rate precluding colonization.

The results of this study do not allow any firm decision as to whether chemical or mechanical factors are more important. The pattern of results shown in Fig. 1 could be explained by chemical factors since it is likely that at this high level the acidity of stomach secretions is able to prevent growth of micro-organisms in the small intestine. However, the results shown in Fig. 2 could equally well be explained by disturbance of chemical or mechanical factors. The alteration in local conditions or the distension which accompanies obstruction of the small intestine could inhibit secretion of an as yet unknown chemical antibacterial substance. But it is also possible and seems more likely that the effect of obstruction on bacterial content of the small intestine could be explained by disturbance of mechanical factors alone, i.e. by the arrest of onward passage of intestinal contents and alteration of motility patterns.

From the results it is clear that parenteral antibiotics do not substantially affect the flora found above an obstruction. However, as the peritoneal swabs in those patients with non-viable bowel showed a flora of the same type as the bowel content, parenteral antibiotics may be of value in preventing peritoneal or blood spread of these organisms or of organisms spilled at operation.

Summary

The bacterial flora of the small intestine in 12 newborn and 13 older children with intestinal obstruction has been studied.

A profuse flora predominantly of faecal type was demonstrated above the point of obstruction when this was below the duodeno-jejunal flexure.

The small intestine below the site of complete obstruction was sterile.

The source of infection above an obstruction is considered to be ingestion and not retrograde spread from the colon.

The antibacterial mechanism of the small intestine is disturbed when the intestinal lumen is obstructed and reasons for this disturbance are briefly discussed.

We would like to thank the surgeons of the Royal Children's Hospital, Melbourne, for their cooperation and also the medical and surgical registrars, particularly Dr. David Danks, for their help.

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FREEZE-DRIED B.C.G.

BY

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Freeze-dried B.C.G. of British manufacture became available for experimental work in 1955. The main reason for introducing it was the need for a vaccine which would retain its potency under conditions of prolonged storage. On reconstitution for injection the vaccine should produce a uniform suspension with minimal clumping, resulting in a uniform viable bacterial count. These properties mean that tests for potency and for sterility can be performed on samples of each batch before distribution, which will be more leisurely as only surface transport is required. Centres using B.C.G. can store stocks instead of depending on week to week supplies and finally, the vaccination lesions can be more uniform and predictable, if the viable count of the vaccines remains constant for anything up to a year or longer. Experimental work in the laboratory has shown that the vaccines made in this country have fulfilled all these requirements (Ungar, Farmer and Muggleton, 1956; Ungar, 1958; Medical Research Council, 1958).

It was essential to show that freeze-dried B.C.G. was safe, would produce acceptable vaccination lesions, a high degree of tuberculin conversion within eight to 12 weeks and a positive tuberculin reaction over prolonged periods in vaccinated subjects. The optimal number of viable organisms to be injected had to be determined in order to achieve a minimal vaccination lesion with practically 100% conversion rate. The most suitable subjects for the initial clinical trials were non-contacts, because failure of conversion or a rapid reversion would not result in serious inconvenience.

Clinical trials using the technique of intradermal injection were conducted in infants by Lorber, Hart, Farmer and Muggleton (1956); Lorber, Farmer, Muggleton, Hart and Menneer (1957); Griffiths and Gaisford (1956), and in children of various ages by Lorber and Menneer (1958) and Alston, Cowell and O'Meara (1958), and in school children (13-14 years) by the Medical Research Council (1958).

These clinical trials established that there was a close correlation between the number of viable organisms injected and the size of the vaccination lesions, the incidence of regional lymph-node involvement and the degree of tuberculin sensitivity following vaccination. It was apparent that reconstituted vaccines containing 10×10^6 organisms per ml. or more were unnecessarily potent and that those containing less than 1×10^6 were not sufficiently antigenic for routine use. It was also shown on controlled trials that the immediate results obtained with freeze-dried vaccines were as good as with the standard Danish liquid vaccine (Lorber *et al.*, 1957; Medical Research Council, 1958) or with the Swedish liquid vaccine (Alston *et al.*, 1958). When the number of viable organisms injected was of similar order, the vaccination lesions and the conversion rates differed very little in subjects given the dry or the liquid vaccines. As the Danish liquid vaccine had proved to be excellent both with regard to the duration of tuberculin sensitivity after vaccination (Griffiths and Gaisford, 1956; Lorber and Menneer, 1959) and its protective value against tuberculous disease in children in intimate contact with infectious tuberculosis (Lorber and Menneer, 1959), it was hoped that the freeze-dried vaccine would eventually prove to be equally efficient in these respects.

The clinical trials quoted above were concerned with the demonstration of tuberculin conversion some weeks after vaccination and with the appearance of the lesions at this stage. Since the research suggested that the best results might be obtained by a vaccine containing between 1×10^6 and 10×10^6 viable organisms per ml. of reconstituted vaccine, the manufacturers marketed such a vaccine. The Ministry accepted this vaccine as suitable for the vaccination of contacts and others and it is estimated that at present this freeze-dried vaccine is used by about half the authorities using B.C.G. in this country.

TABLE
RESULTS OF VACCINATION WITH FREEZE DRIED B.C.G. VACCINE
SIX TO 12 WEEKS AND ONE YEAR AFTER VACCINATION

Batch No.	Viability Count/ml.	Results Six to 12 Weeks after Vaccination				Tuberculin Test One Year after Vaccination			
		Method of Tuberculin Testing	No. Completing Tests	No. (%) Tuberculin Positive	Local Lesion (mm.)		Method	No. Completing Test	No. (%) Positive
					Range	Average			
<i>Experimental Batches</i>									
50	0.14×10^6	10 T.U. O.T.	92	52 (56.5)	1-15	6	{ 10 T.U. O.T. 10 T.U. BCG(T) 100 T.U. O.T. Jelly Heaf 100 T.U. O.T.	83 111 240	83 (100) 109 (98) 240 (100)
77	23×10^6	10 T.U. O.T.	114	99 (86.8)	2-28	13			
93a	11×10^6	{ 10 T.U. O.T. 10 T.U. BCG(T) 100 T.U. O.T.	315	312 (99)	2-28	10			
<i>Commercially produced batches: Annual tests completed</i>									
143	8×10^6	{ Jelly Heaf 100 T.U. O.T.	40	40 (100)	—	15	„	35	35 (100)
132 142 162 166 190	$2.4-5 \times 10^6$	„	789	785 (99.5)	3-20	6	„	536	536 (100)
<i>Annual tests not yet completed</i>									
193 200 240 253 263 270	4.5×10^6	„	274	274 (100)	2-15	6			
Total								1,005	1,003 (99.8)

BCG (T) = BCG Tuberculin (Lorber, 1957)

Present Study

The purpose of this paper is to report on the efficiency of this commercially available freeze-dried B.C.G. and to extend our previous observations by reporting on the follow-up of children who were re-examined one year after vaccination. Altogether 1,103 children (mostly contacts) had completed the vaccination procedure after the completion of our previous trials. These were all vaccinated with commercially available batches. In addition we recalled for examination and tuberculin tested 1,005 children one year after their vaccination. Of these, 434 were vaccinated earlier with experimental batches of widely differing viability counts (0.1×10^6 to 23×10^6 per ml.), and 571 with commercial batches of far more uniform viability counts (2.4×10^6 to 8.0×10^6 per ml.) (see Table).

Vaccination and tuberculin testing technique. All subjects had been shown to be tuberculin negative a minimum of six weeks after exposure to tuberculous infection. They were then vaccinated with B.C.G. and were kept away from such exposure for a further period until tuberculin conversion was demonstrated six to eight weeks later. Freshly reconstituted vaccine, 0.1 ml. was injected intradermally at the level of the insertion of the left deltoid muscle.

The routine tuberculin testing consisted of the tuberculin jelly test, which was applied by the Health Visitors in the children's own home four days before they attended the clinic. This was carried out before vaccination and six to eight weeks after it. If the result was doubtful, or if for some reason the jelly test had not been performed, or if the result was negative after vaccination, the Heaf test was used and read 96 hours later. Those still negative were finally tested with 100 T.U. (Mantoux 1/100). The same procedure was used one year after vaccination.

The vaccination lesions. A small group of 40 children was vaccinated with a batch containing 8×10^6 viable organisms per ml. The lesions in these were unduly large, averaging 15 mm. in diameter and crusting frequently occurred. The remaining 1,063 children were vaccinated with batches containing $2.4-5.0 \times 10^6$ viable organisms per ml. The vaccination lesions in all these were very acceptable, with an average diameter of induration of 6 mm. No ulceration was seen in any and the regional lymph glands in the axilla did not become palpable. One year after vaccination there was only a shallow colourless depression.

Tuberculin tests. All but four of the 1,103 (99.6%) children vaccinated with these commercial

batches became tuberculin positive six to eight weeks after vaccination and only one in 10 of those who had a jelly test required a Heaf test to prove tuberculin conversion.

Of the 434 children who were vaccinated earlier with experimental batches, 432 (99.7%) were tuberculin positive a year after vaccination and the only two negative reactors have not been tested either with the Heaf test or with 100 T.U. intradermally. It is of great interest that 83 children who had been vaccinated with the weakest vaccine containing only 0.14×10^6 viable organisms per ml., and whose post-vaccination conversion rate was only about 56%, all became tuberculin positive one year after vaccination.

Conclusion and Summary

Freeze-dried B.C.G. has been proved in the laboratory to be of uniform consistency with a viable bacterial count which, if kept in a cool place, persists unaltered in the dry state for a year or longer. It is safe and convenient to use. Suspensions, 0.1 ml., containing approximately 2.5×10^6 organisms per ml. were injected intradermally into over 1,000 children. The result was a papule, averaging 6 mm. in diameter. There was neither ulceration nor enlargement of the regional lymph-nodes. Tuberculin conversion was demonstrated in virtually 100% six to eight weeks after vaccination and a positive tuberculin reaction was maintained for up to at least one year after vaccination. In the case of others who were vaccinated with

weaker vaccines the proportion of positive reactors increased with time, indicating the probability that prolonged tuberculin sensitivity will be produced with the freeze-dried vaccine in current use.

It is a great pleasure to thank Dr. L. Ungar and Dr. P. W. Muggleton of Glaxo Laboratories Ltd. for their continued help with these investigations, for supplying us with the laboratory data and for providing the vaccines; the Chest Physicians of Sheffield for referring so many patients to us, Dr. Llywelyn Roberts, Medical Officer of Health, Miss I. Littlewood, Superintendent Health Visitor, and her staff of the City of Sheffield, for their assistance, Professor R. S. Illingworth for his criticism and the Tuberculosis Research Fund of the University of Sheffield for a research grant to one of us (P.C.M.).

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A CASE OF OSTEOPETROSIS (ALBERS-SCHÖNBERG) WITH INTERCURRENT PNEUMOCYSTIS PNEUMONITIS

BY

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Albers-Schönberg (1904, 1907) defined the clinical and radiological features of a sclerosing disease of bone for which Karshner (1926) suggested the term osteopetrosis. As published cases of the disease accumulated, two types came to be distinguished (McCune and Bradley, 1934; Harnapp, 1937; Nussey, 1938; Zetterström, 1958). The first, or clinically 'malignant' type may be characterized by a refractory and often leucoerythroblastic anaemia, enlargement of liver, spleen and lymph nodes, a liability to multiple fractures, and death in infancy or early childhood. In the second or clinically 'benign' type, more commonly seen in adults, anaemia is mild and the osteosclerosis, though often severe, may yet be symptomless.

In the more severe forms of osteopetrosis, intercurrent infection, particularly of the respiratory tract, is a serious hazard. The case to be reported here, an example of the 'malignant' type, succumbed to an interstitial 'plasma cell' pneumonitis.

Though this unusual pneumonitis has been recognized for many years in central Europe its aetiology had been obscure until 1951. In that year Vaněk, in Czechoslovakia, identified *Pneumocystis carinii* in the lungs of all of a series of 16 fatal cases of this disease. In a series of papers (Vaněk, 1951; Vaněk and Jírovec, 1952; Vaněk, Jírovec and Lukeš, 1953) evidence was presented that *Pneumocystis carinii* was the causal agent of interstitial plasma cell pneumonitis. Nevertheless, Deamer and Zollinger (1953), who first drew American attention to the disease, concluded that it was probably a viral one; they dismissed a fungal or protozoal agent as unlikely. Baar (1955) reported the first case to be observed in England and subscribed to the hypothesis that *Pneumocystis carinii* was the pathogen. The subject is comprehensively reviewed by Gajdusek (1957).

Pneumocystis carinii pneumonitis has been found associated with congenital agammaglobulinaemia (Hutchison, 1955; Bird and Thomson, 1957;

Russell, 1959), cytomegalic inclusion disease (Baar, 1955; Hamperl, 1956), and neoplastic disease of the lympho-reticular tissue in both children and adults (Vaněk, 1952; Jírovec and Vaněk, 1954; Le Tan Vinh, 1954; Hamperl, 1956). Association with Albers-Schönberg's osteopetrosis has apparently not been reported before.

Case Report

W.T. (Reg. No. R.I. 250922), was a male infant, the first-born and only child of healthy unrelated parents. Pregnancy and labour had been uneventful. In the first 24 hours bruises were noticed on his upper lip and on several toes. These bruises disappeared within a few days. On the second day he regurgitated blood-flecked milk. Nothing further happened until the 13th day when another bruise appeared on his right leg and a small haematoma-like swelling was found on his umbilicus. As these subsided others appeared near the anus and over the chest wall. He became progressively paler.

On admission to hospital at 3 weeks of age, he was pale but reasonably vigorous and not acutely ill. He weighed 5 lb. 14 oz. There were bruises on the left chest, right thigh, right groin and umbilicus. A small abscess cavity was found close to the anus posteriorly. The liver was palpated about a finger breadth below the costal margin, and though the spleen was not palpable at first it could be tipped after four days and readily palpated within a week. Apart from these there were no unusual clinical findings.

Laboratory Investigations on Admission. Hb 45% (6.6 g./100 ml.); erythrocytes showed some anisocytosis and poikilocytosis; there were no Heinz bodies. Leucocytes 34,000/c.mm. (blast cells 340, promyelocytes 700, myelocytes 1,400, band forms 2,700, segmented neutrophils 12,000, eosinophils 700, monocytes 3,400, lymphocytes 13,000); reticulocytes 1.0%; normoblasts (occasionally in mitosis) 5/100 leucocytes. There was, therefore, a severe leucoerythroblastic anaemia (Fig. 1). In addition, the platelet count (Lempert) gave 21,000/c.mm. (a proportion of which were abnormal giant forms) and the bleeding time (Ivy) was prolonged to 13 minutes. Clotting time (Dale and Laidlaw) was normal at 1 min. 50 sec. and the

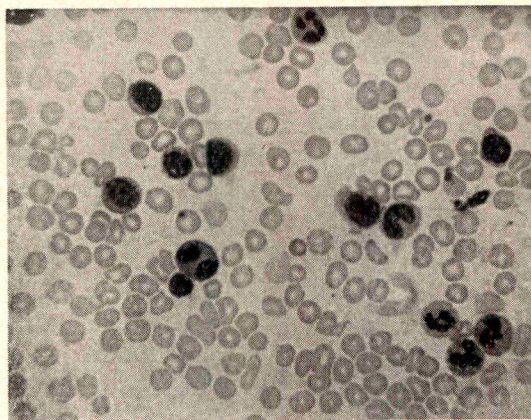


FIG. 1.—Peripheral blood film showing immature erythroid and myeloid cells. May-Gruenwald-Giemsa $\times 584$.

tourniquet test was negative. The blood group was O Rh positive. The direct Coombs test was negative and the mother's serum was found to be compatible with the patient's erythrocytes. No platelet agglutinins could be demonstrated in the mother's serum. The

toxoplasma dye test dilution was 1/6 and the toxoplasma complement fixation test was negative. Wassermann and Kahn reactions were negative in both mother and infant. Puncture of the tibial marrow was attempted unsuccessfully.

Progress in Hospital. Towards the end of the first week in hospital the perineal abscess was evacuated. A scalp vein transfusion of 110 ml. of blood brought the Hb level to 96% (14.2 g./100 ml.). After this there was some clinical improvement, but within 17 days the Hb had fallen again to 58% (8.6 g./100 ml.), i.e. at the rate of about 2.6% (0.3 g./100 ml.) daily although there was no haemorrhage during this period. The fluctuations in the haemoglobin levels are shown in Fig. 2 in relation to blood transfusion and blood loss. Serial leucocyte and platelet levels are shown in the Table.

Further scalp-vein transfusion of 100 ml. of blood restored the Hb to 96% (14.2 g./100 ml.). Five days later he developed epistaxis and began to ooze blood from the gums. About this time it was observed that any skin punctures tended to bleed excessively. During the next three weeks the Hb fell steadily to 46% (6.8 g./100 ml.) necessitating blood transfusion once again. A transfusion of 150 ml. was therefore given by an

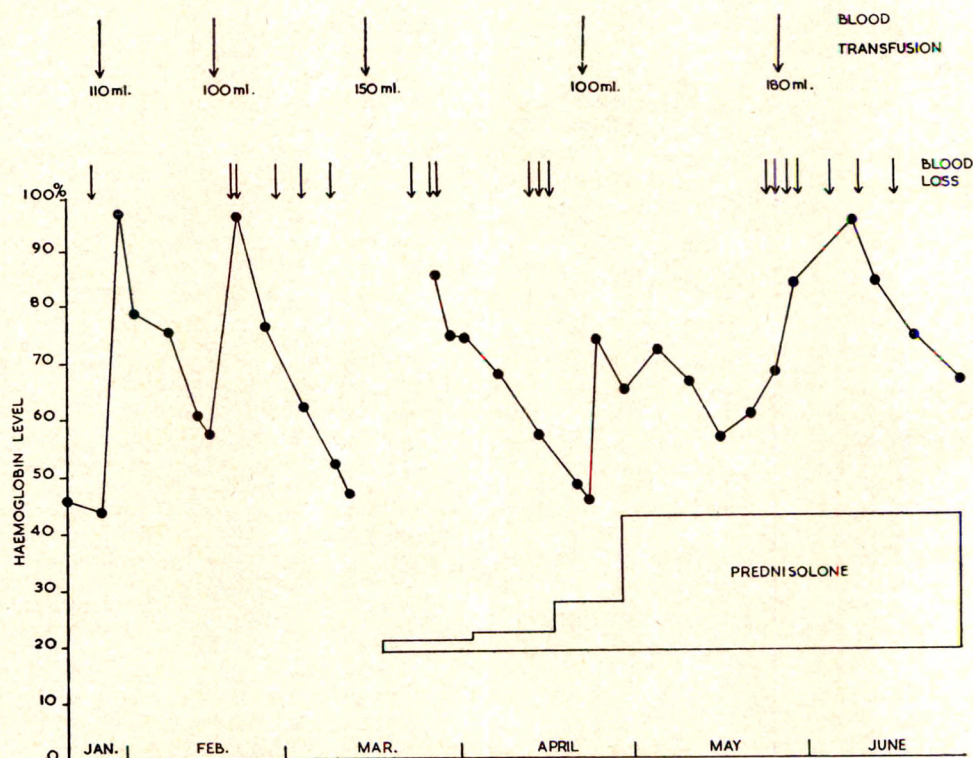


FIG. 2.—Serial haemoglobin levels. Blood transfusions and episodes of bleeding are arrowed.

TABLE
SERIAL LEUCOCYTE AND PLATELET LEVELS

Date	Treatment	Hb (%)	Reticulo-cytes (%)	Normo-blasts/c.mm.	Plate-lets/c.mm.	W.B.C./c.mm.	Remarks
Jan. 23		45	1.0	1,700	21,000	34,000	
Jan. 28	Blood transfusion 110 ml.	43	2.2	5,800	20,000	64,500	
Jan. 31		96	—	1,300	67,000	66,000	
Feb. 5		76	—	1,000	61,000	48,000	
Feb. 10		75	—	280	48,000	28,000	
Feb. 14		60	—	—	102,000	40,000	Leukaemoid picture with about 1% blast cells; 2% promyelocytes; 5% myelocytes
Feb. 17		58	—	—	—	—	
Feb. 19	Blood transfusion 100 ml.	96	—	380	25,000	38,000	
Feb. 21		62	—	310	14,000	31,000	
Mar. 4		52	—	—	45,000	50,000	
Mar. 10		46	2.2	360	51,000	36,000	
Mar. 13	Blood transfusion 150 ml.	84	—	—	50,000	28,500	
Mar. 18	Prednisolone 1 mg. twice daily	74	—	—	102,000	36,000	
Mar. 28		56	—	2,850	91,000	57,000	
April 3	Prednisolone 1 mg. three times daily	48	—	—	124,000	57,000	Disappearance of blast cells and promyelocytes; neutrophil leucocytosis with 1-3% myelocytes and 20,000-30,000 lymphocytes/c.mm.
April 15	Prednisolone 2 mg. three times daily	74	—	2,940	145,000	98,000	
April 17		67	3.8	4,000	240,000	80,000	
April 22	Blood transfusion 100 ml.	62	—	880	190,000	22,000	
April 24		84	—	—	130,000	28,000	
April 25	Prednisolone 4 mg. four times daily	95	—	—	—	—	
April 29		84	10	1,800	+	45,000	
May 12	Blood transfusion 180 ml.	75	—	3,050	+	77,000	
May 23							
May 28							
May 31							
June 9							
June 13							
June 20							

antecubital vein. Meanwhile the spleen was noted to be enlarging gradually. Septic skin lesions on the head and on the left hand were treated with oral terramycin.

Towards the end of the second month in hospital it was decided to treat him with prednisolone, at first in a dose of 1 mg. twice daily, increasing over the next four weeks to a maximum of 4 mg. four times a day. With this his general condition improved considerably, although he continued to show purpuric lesions over the skin and abdomen. The platelet count began to rise shortly after administration of prednisolone and reached the normal level of 240,000/c.mm. during the subsequent eight weeks.

Nevertheless, episodes of bleeding continued. Ten days after the start of prednisolone treatment severe epistaxis began again and continued in bouts during the next three weeks. It was eventually controlled by intranasal adrenaline sprays. By this time Hb level had fallen to 48% (7.1 g./100 ml.), now at the rather slower rate of 1.4% daily. A further blood transfusion of 100 ml. was given.

Marrow puncture was attempted again and yielded, with some difficulty, a hypocellular but otherwise normal marrow. As a fortnight passed without blood loss, and he was in good general condition, he was discharged home on 16 mg. of prednisolone daily.

While at home he caught a 'cold' and developed a cough. He went off his feeds, which he had been taking well till then. He was therefore re-admitted, now at the age of 4½ months. On examination his temperature was 99.6° F. and his breathing rate was 64 per minute.

His colour was dusky and he looked ill. There was some nasal discharge and reddening of the fauces.

His breathing was grunting in character; the alae nasi were working and there was some intercostal recession. However, the percussion note and the breath sounds were normal and there were no adventitious. The liver and spleen were still palpable but now smaller. A chest radiograph showed no definite radiological lesion.

Two days later there was a fresh crop of purpuric lesions on his abdomen, although his platelet count was now normal. He maintained a persistent low-grade fever with some cough but no physical signs in the chest. After a further transfusion of 180 ml. blood, which brought his Hb level from 62% (9.1 g./100 ml.) to 95% (14.1 g./100 ml.) his general condition improved though his breathing remained rapid and there was some further bleeding from nose and rectum. At this time the spleen had receded so that it could only be tipped. He was feeding well and seemed happy. He was discharged once again on prednisolone and oral erythromycin.

He was re-admitted five days later because his cough had become worse and he had gone off his feeds again. On examination he was pale and ill and had a weak cry. His breathing was still rapid though his chest appeared clinically and radiologically clear. The liver was palpable two or three finger breadths below the costal margin; the spleen could not be felt. He remained somewhat febrile, breathing at the rate of 60-120/min. On the 10th day of this admission he died suddenly at the age of 6 months.

Morbid Anatomy. At autopsy (P.M. 512/58) the following were the main macroscopical findings:

MACROSCOPICAL FINDINGS

Lungs. The lungs failed to retract as the chest was opened. Both were of a mottled café-au-lait colour. They presented a curious, vaguely nodular consolidation which was more marked in the lower lobes. The cut surfaces were dry and showed small scattered yellowish-white areas. The tracheobronchial tree was normal.

Liver. The liver (196 g.) appeared normal in size, consistency and colour.

Spleen and lymphoid tissue. The spleen (16 g.) was rather firm, but not appreciably enlarged. The cut surfaces appeared normal. Lymph nodes in general were inconspicuous. The thymus was involuted.

Bones. The calvarium appeared to be of average thickness and density. The features of the base of the skull were not detectably abnormal and the middle ears were opened without difficulty. Both femora were shorter than normal and very slightly clubbed. They proved very difficult to cut because of a dense sclerosis of the medullae. A vertebral body was similarly sclerosed. These excised bones and the remainder of the skeleton were radiographed and showed the following features: There was an overall increase in the density of the femur as compared with a normal control (Fig. 3).

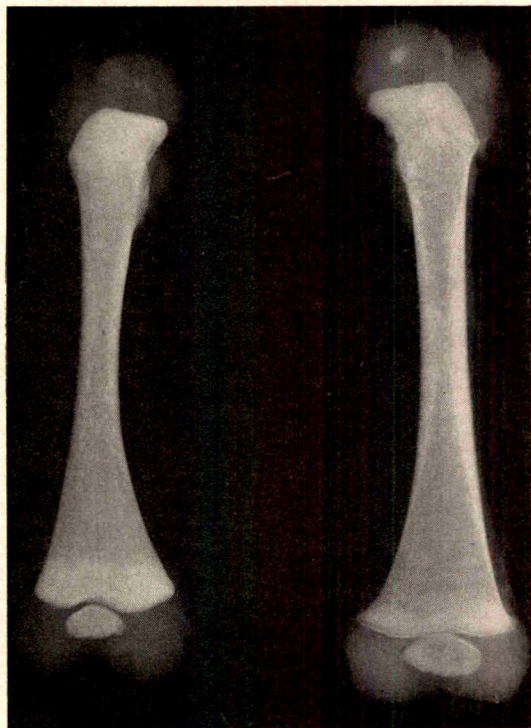


FIG. 3.—Femur showing osteopetrosis compared with normal femur of similar age.

Trabecular detail was obscured and marrow spaces appeared small. Particularly dense transverse bands occupied the metaphyseal growth zone; that in the distal metaphysis of the femur measured more than 1 cm. in the axis of the bone. The distal epiphyseal centre of ossification was rather small and dense. Very similar changes were visible symmetrically in tibiae, fibulae, humeri, radii and ulnae. Clubbing was more obvious at the distal ends of the radii and the tibiae than elsewhere. Similar but slighter bands of metaphyseal density were visible in metacarpal bones. Pelvic bones, vertebrae, ribs, clavicles and scapulae showed overall increase in density. In carpal, tarsal and skull bones the changes were too slight for dependable assessment.

HISTOLOGICAL FINDINGS

The Lungs. Both lungs showed an overall interstitial fibrosis. This was mainly due to an increase in reticulin but occasional collagen bundles contributed to it. The thickened alveolar walls and septa were infiltrated by mononuclear cells, some of which resembled plasma cells. Polymorphonuclear leucocytes were not seen in significant numbers. The alveoli and alveolar ducts in most areas contained an eosinophilic foamy material which was bordered in some alveoli by coalescing macrophages (Fig. 4). This material gave the tinctorial reactions of a polysaccharide (periodic acid-Schiff) through which small chromatin bodies (Giemsa; Feulgen) were distributed. It did not contain fibrin (Mallory's phototungstic acid-haematoxylin) or mucus (mucicarmine). Silver impregnation (Hortega) confirmed the presence of morphologically typical *Pneumocystis carinii* (Fig. 5). Viral studies were not made. The appearances were those of an interstitial pneumonitis in which the only detectable organism was the *Pneumocystis carinii*.

The Liver. The parenchymal cells contained rather large quantities of stainable iron.

The Spleen. The sinusoids were prominent and their littoral cells were plump. Many sinusoids contained large pale free macrophages. These phagocytes contained nuclei or fragments of nuclear material, a good deal of iron pigment and an occasional red cell ghost (Fig. 6). There was some excess of reticulin in the stroma. No evidence of haemopoiesis was found.

Lymph Nodes. These showed a fairly well marked excess of reticulin. Active haemopoiesis was visible in some nodes.

Bones. The disturbances affected endochondral ossification only mildly. Those seen in the femur will be taken as illustrative. *Mutatis mutandis*, similar changes were seen in other sites. The most striking feature was a massive persistence of calcified cartilage (the primary spongiosa) as irregular longitudinal islands, bordered and occasionally penetrated by immature new bone (Fig. 7). In the electron microscope the calcification of this cartilage was seen to be patchy but often unusually dense. The metaphyses were thus packed with stout anastomosing trabeculae of unresorbed primary elements and the enclosed marrow spaces were correspondingly small. This thicket extended in a modified form to the

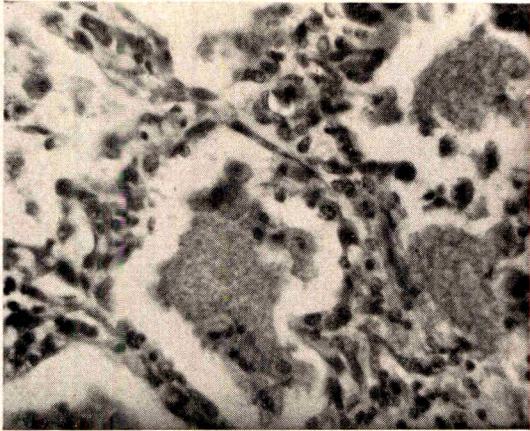


FIG. 4.—A group of pulmonary alveoli showing thickened alveolar walls and the foamy material of *Pneumocystis carinii*. H. and E. $\times 345$.

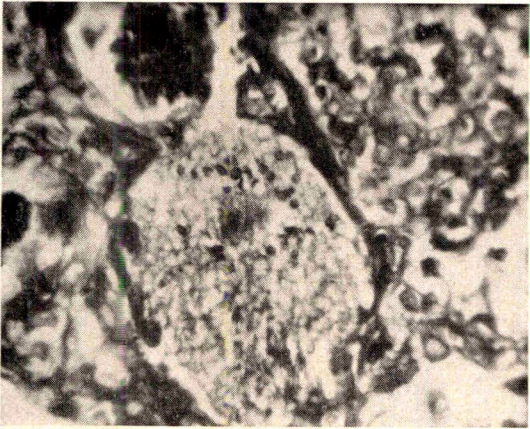


FIG. 5.—*Pneumocystis carinii* as demonstrated by silver impregnation. H Ortega $\times 447$.

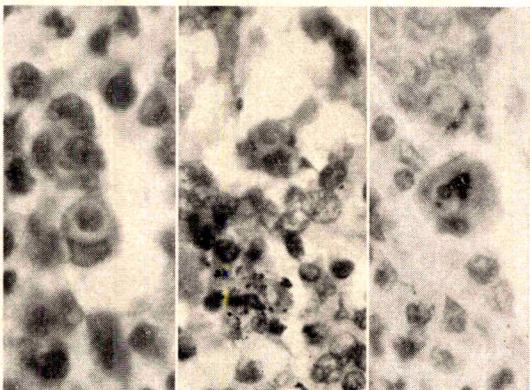


FIG. 6.—Composite picture of three splenic fields showing phagocytosis of a nucleated cell, an erythrocyte and some cell debris. H. and E. $\times 620$.

diaphysis. Here spongy bone was still excessive but the cartilaginous component was diminished and the marrow spaces were considerably larger. In polarized light much of the new bone bordering the persistent cartilage showed normal lamellation. On the other hand the bone which had formed within vacated cartilage cell capsules showed no orientation of its collagen fibres. Both varieties of new bone were Schiff-positive.



FIG. 7.—Metaphyseal growth zone of femur, showing abnormal persistence of cartilage and formation of dense chondro-osseous mosaic. H. and E. $\times 172$.

Periosteal ossification was less disturbed but Haversian systems appeared poorly formed in many areas. Occasionally the cortex included some persistent cartilage and immature bone.

Bone Marrow. The small marrow spaces in the growth zone contained an excess of reticulin through which ran thick-walled capillaries. Normal bone similarly stained showed more delicate mesenchyme and larger thin-walled vessels in this region. The osteopetrotic metaphysis appeared less vascular than usual and the capillaries morphologically abnormal.

Haemopoietic tissue occupied the marrow spaces in the remainder of the bone. Erythropoiesis and leucopoiesis were both in progress and occasional megakaryocytes were seen. There appeared to be a mild hyperplasia of myelocytes, and colonies of these cells were especially noted along the adventitia of small

arterioles and along the borders of many trabeculae. Fat cells were very scanty. This marrow differed from normal marrow, similarly stained, in being more densely cellular and in not showing the usual prominence of marrow sinusoids. Where sinusoids could be discovered they contained both erythropoietic and leucopoietic cells, an appearance which suggested intravascular haemopoiesis.

Other Organs. Apart from some foci of calcium deposition in the medulla of the kidneys other organs were unremarkable.

Discussion

Generalized osteosclerosis in infancy may be secondary to congenital syphilis, heavy metal poisoning, excessive dosage with vitamin D and perhaps leukaemia. Of these diseases only leukaemia merits consideration in the present case. However, leukaemia typically causes osteolysis and on the rare occasions when it causes sclerosis this is found to be due to direct metaplasia of reticular or collagenous structures into woven bone (Windholz and Foster, 1949). Therefore this disease also may be ruled out.

Albers-Schönberg's osteopetrosis, on the other hand, accounts satisfactorily for both the clinical and the pathological findings. The clinical features closely resemble those of cases reported by Pines and Lederer (1947) and Turano, Fagan and Corbo (1954). The pathological structure of the bone is typical of osteopetrosis. As in previously reported cases the most obvious and probably the primary abnormality is a persistence of the calcified cartilaginous scaffolding upon which new bone is built. Layers of new Schiff-positive bone are seen on the surfaces of the cartilage masses, and tinctorially similar bone appears in the spaces from which cartilage cells have vanished. Normally a provisional design of this sort undergoes considerable modification. Most spongy bone and all remnants of cartilage are resorbed from the marrow cavity and increasingly lamellated bone is incorporated peripherally into the cortex. The appearances in the present case may be interpreted as the effect of a retarded remodelling process. Relatively little lamellar bone is present. Islands of immature bone, of which the collagen is unorientated, form a mosaic with the persistent irregularly calcified cartilage. The tensile strength of such tissue must be well below normal in spite of its apparent solidity.

Either the cartilage matrix is unusually resistant to remodelling or the mechanism of remodelling is defective. Of course, both factors may cooperate, but there is no evidence at present of abnormal cartilage matrix. On the other hand the vascular

metaphyseal mesenchyme, which plays a major part in resorptive modelling, may well be at fault. Evidence in favour of this thesis may be found in the experimental work of Trueta and Amato (1960). They found that interruption of the blood supply to the metaphysis of growing bone inhibited the resorption of chondro-osseous tissue and delayed the formation of final bone. Large zones of calcified cartilage and preliminary bone remained at a level in the metaphysis where, normally, remodelling is taking place.

Many authors (McCune and Bradley, 1934; Lamb and Jackson, 1938; Clifton, Frank and Freeman, 1938; Pines and Lederer, 1947) have adopted Klemperer's (1931) suggestion that the fundamental disturbance in Albers-Schönberg's disease may lie in the undifferentiated mesenchymal anlage, the common progenitor of bone and marrow. Osteogenesis and haemopoiesis, according to this hypothesis, are both blighted by a prior defect involving mainly the former process in benign cases and the latter in malignant. But in the present case histological study did not suggest an intrinsic defect of osteogenesis. Similarly, Zetterström's (1958) biophysical studies led him to the conclusion that osteopetrotic bone comprises all those types of skeletal tissue which appear during the normal development of bone, the abnormality being a failure of normal removal. Furthermore, Pines and Lederer (1947) noted that the skeleton in general was poorly vascularized but that bone and marrow approached normal at sites of enhanced vascularity. In the present case also an impression of poor skeletal vascularity and of abnormal vessel structure was gained. The hypothesis of mesenchymal perversion might therefore be restated in a form which postulates abnormal vasoformation rather than abnormal osteogenesis. This view would suppose a mesenchymal defect which may involve predominantly the vascular remodelling tissue in benign osteopetrosis or the closely allied haemopoietic tissue in malignant osteopetrosis.

As in the cases of Lamb and Jackson (1938), Kramer and Halpert (1939), and others, the refractory anaemia could certainly not have been due to a simple crowding out of otherwise healthy haemopoietic tissue, as is commonly supposed to happen. In the present case the volume of the marrow cavity was estimated and found to be fully 70% of normal. Moreover, the marrow tissue was a good deal more cellular than normal. Therefore a merely mechanical theory of dyshaemopoiesis is plainly inadequate.

Though one may hypothetically attribute the leucoerythroblastic anaemia to a dysplasia of

marrow tissue other mechanisms must also be evaluated. Skin sepsis and episodic haemorrhage must have played their parts, though the haemoglobin level continued to fall on occasions when neither was operative. Red cell destruction probably played a major part. Zetterström (1958), using a radioactive chromium technique, found a mean red cell survival time of 35-40 days in one of his cases, a patient aged 10 years. With colleagues (Engfeldt, Karlberg and Zetterström, 1955) he found a shortened survival time of both native and donor cells in another patient aged 6 years, though this observation was not expressed quantitatively. He therefore suggested that the anaemia may be due to hypersplenism. Loeb, Moore and Dubach (1953) have found this to be true of certain cases of myelosclerosis; in these, splenectomy restored a shortened red cell survival time to normal. Sjölin (1959) reported four cases of malignant osteopetrosis in each of which accelerated red cell destruction was proved isotopically. Splenectomy improved the haemoglobin level in all cases, though the red cell survival time was not always restored permanently to normal. The platelet count, which had been low in all four cases, returned to normal and reticulocytosis diminished. The author concluded that hypersplenism was an important feature of malignant osteopetrosis.

Though no direct estimate of red cell survival was made in the present case the concept of hypersplenism is apposite. Admittedly a cellular marrow is not necessarily a productive one but the abundance of maturing cells, together with the presence of normoblasts in the peripheral blood and a continuous reticulocytosis, suggest that the anaemia was not wholly due to a failure of production. Furthermore, the steep fall of haemoglobin level (2.6% daily before administration of prednisolone), the marked haemosiderosis of liver and spleen (partly due to transfusion, no doubt) and the apparently enhanced activity of splenic phagocytes suggest excessive destruction.

The leukaemoid reaction is commonly supposed to be an expression of extramedullary haemopoiesis, at least in part; immature cells escape into the blood stream more easily from ectopic sites in soft organs. But the extent of haemopoiesis in the tissues at autopsy was surprisingly slight, as in many previously reported cases (Reiche, 1929, quoted by McCune and Bradley, 1931; Pease, DeSanctis and Alter, 1934; Lamb and Jackson, 1938). An alternative cause may lie again in dysfunction of the bone marrow itself, for which the observed myelocytic hyperplasia and the apparently intrasinusoidal haemopoiesis afford some evidence.

The tendency to haemorrhage is not completely explicable by thrombocytopenia and may have had a thrombasthenic component. Siegel, Friedman and Schwartz (1957) reported a patient with osteogenesis imperfecta tarda and an associated haemorrhagic diathesis due to increased capillary fragility and abnormal platelet function. These authors believed that their case represented a congenital defect involving two tissues of mesenchymal origin, the osseous system and the platelets. In the present case morphologically abnormal (giant) platelets were present and the haemorrhagic tendency persisted after the total platelet count had returned to normal.

Treatment with prednisolone brought about some improvement in the child's general condition and appeared both to decelerate the fall of haemoglobin level and to correct the leukaemoid state. The sclerosing process in the skeleton, on the other hand, was not abated. This is surprising, in view of the experimental findings of Baker and Ingle (1948) that 11-oxysteroids inhibited the proliferation of cartilage cells and brought about a profound and general atrophy of osteoblasts, so that the resorption of metaphyseal trabeculae occurred more rapidly than their formation. One might have expected prednisolone to be the rational treatment of osteopetrosis.

Prednisolone may have predisposed to infection with *Pneumocystis carinii* by further depression of a naturally low resistance. The result was the development of an interstitial pneumonitis of a type usually found in premature weakly infants or complicating diseases of the lymphoreticular system. It is of interest, furthermore, that prior and current treatment with prednisolone did not inhibit the development of a marked interstitial pulmonary fibrosis.

Summary

A case of 'malignant' osteopetrosis is reported. The patient presented in the neonatal period suffering from a leuco-erythroblastic anaemia complicated by a haemorrhagic tendency, and died at the age of 6 months primarily of an interstitial pneumonitis due to *Pneumocystis carinii*. An attempt is made to illustrate some of the problematical features of osteopetrosis. Future research might be directed towards studying the vascularity of the bone, evaluating the respective roles of dyshaemopoiesis and increased red cell destruction, and determining the adequacy of platelet function.

My thanks are due to Dr. Victoria Smallpeice for permission to publish this case, to Dr. A. H. T. Robb-Smith and Professor J. Trueta for critical advice, to many colleagues for their stimulating views, and to

Mrs. D. Jackson and Mr. E. L. Tugwell for the photographs.

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INTRAUTERINE BLOOD TRANSFER BETWEEN UNIOVULAR TWINS

BY

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The non-haemolytic anaemias of the newborn have recently attracted the attention of many investigators. Of particular interest has been the anaemia due to occult blood loss of the foetus into the maternal circulation (Wiener, 1948; Chown, 1954; Ganson, 1957).

Another type of intrauterine occult blood loss has been recognized in the last few years as being due to transfusion of blood from one uniovular twin to the other through anastomotic vessels in the placenta (Herlitz, 1942; Bosma, 1954; Klingberg, Jones, Allan and Dempsey, 1955; Bergstedt, 1957; Betke, Deibel and Schlicht, 1958; Sacks, 1959). The present paper describes a similar case and our attempts to rectify it.

Case Report

The mother, a multigravida, 29 years of age, gave birth eight weeks before term to twin girls, the first weighing 1,250 g. and the second 1,500 g. Both babies breathed and cried immediately after delivery. A striking difference in colour was noticed; the first twin (A) appeared flushed and red and the second (B) was pale without any other signs of anoxia or shock. Venous blood was examined six hours after birth and a marked difference in the Hb and R.B.C. content was found (twin A: Hb 27.8 g. per 100 ml., R.B.C. 9,000,000 per c.mm.; twin B: Hb 8.2 g. per 100 ml., R.B.C. 2,600,000 per c.mm.). As it became evident that there had been intrauterine transfusion of blood from twin B to twin A, we decided to correct this unequal share of Hb. Eight hours after birth polyvinyl exchange-transfusion catheters were introduced into the umbilical vein of the babies. The venous pressure was found at the same level of 6-8 cm. in both twins. Blood was withdrawn in amounts of 5 ml. from the plethoric twin and was immediately given to twin B. No anticoagulant was used, but each catheter, while not used, was filled with a solution of normal saline containing heparine (1,000 units to one litre). In all, 25 ml. of blood was removed from twin A and transfused into twin B. Both twins tolerated the procedure well and we could record no change in the venous pressure or cardiac rate. As this

first transfer of blood was not sufficient to bring the haemoglobin values near enough to normal the procedure was repeated 31 hours after birth when a further 25 ml. of blood was transferred from twin A to twin B. Full haematological details are recorded in Table 1.

The clinical condition of both babies continued to be good until the fifth day when twin A developed broncho-pneumonia and died two days later in spite of treatment with antibiotics. At necropsy the diagnosis of broncho-pneumonia was confirmed. The other twin continued to thrive and develop normally.

As soon as the diagnosis of intrauterine transfer of blood was made the placenta was examined. This was a single-ovum, monochorial, diamniotic placenta, weighing 680 g. One of the cords had a marginal insertion and its vessels spread over the larger part of the placenta. The insertion of the other cord was membranous and three of its vessels were found ruptured. By that time it was impossible to find out to which of the twins each cord belonged. A large yellow infarct measuring 5 × 6 cm. was seen in the periphery and between the two parts of the placenta. No difference in colour or fullness of the vessels between the two parts could be seen. The rupture of the cord vessels prevented us from performing a full 'milk test'. Nevertheless, neither by naked eye nor by injection of fluid through the other cord could we see a major anastomosis.

TABLE 1
BLOOD DATA OF THE TWINS

	Twin A	Twin B
Birth weight in grams	1,250	1,500
Colour at birth	Dark red	Very pale
Blood type	A, D	A, D
Venous blood at 6 hours	Hb g./100 ml. 27.8 (Haematocrit (%)) 82	8.27 24
	Hb g./100 ml. 23.6 (Haematocrit (%)) 74	7.6 22
Blood from umbilical vein at 8 hours	R.B.C.s per mm. ³ 7,900,000 Reticulocytes (%) 6.5 Erythroblasts per 100 W.B.C. 4	2,600,000 18 67
	Foetal Hb (%) 87.3	83.2
Venous blood at 22 hours	Hb g./100 ml. 21.9 (Haematocrit (%)) 72	10.7 34
Venous blood 3rd day	Hb g./100 ml. —	16.5
Venous blood 5th day	Hb g./100 ml. 18.67	—

TABLE 2
DATA FROM REPORTED CASES OF INTRAUTERINE BLOOD TRANSFER

Author		Sex of Twins	Order of Birth		Birth Weight (g.)		Initial Hb (g./100 ml.)		Icterus		Treatment		Outcome	
			A	B	A	B	A	B	A	B	A	B	A	B
Herlitz (1942)	1	M	II	I	2,580	1,580	160%	50%	None	None	None	Oral iron	A + W	A + W
Herlitz (1942)	2	F	I	II	3,030	2,220	200%	65%	None	None	None	Oral iron	A + W	A + W
Bosma (1954)		?	?	?	?	?	31	4	Marked	?	None	?	Kernik- terus	?
Klingberg <i>et al.</i> (1955)	..	F	I	II	2,690	1,770	25.2	3.7	Moderate (S.B.12.3)	None	Removal of 100 ml.	Exch. transf.	A + W	A + W
Bergstedt (1957)	..	F	I	II	3,030	1,810	23.6	13.6	Marked (S.B.23.5)	Slight	None	Oral iron	A + W	A + W
Betke <i>et al.</i> (1958)		M	I	II	2,600	2,130	24.6	9.5	Marked (S.B.22.4)	Slight (S.B. 7.1)	None	Trans- fusion iron, etc.	A + W	A + W
Sacks (1959)	1	M	II	I	2,084	1,431	24	5.5	Marked	None	Bleeding attempted	Trans- fusion	Kernik- terus	Cerebral palsy
Sacks (1959)	2	M	II	I	1,843	1,424	30	18	—	None	Removal of 60 ml.	Trans- fusion later	Died atel- ectasis	A + W
Sacks (1959)	3	F	I	II	2,523	2,041	33	12.8	Moderate (S.B.11.5)	None	Removal of 75 ml.	None	A + W	A + W
Sacks (1959)	4	F	II	I	1,163	1,021	27	15	—	—	—	—	Died at 16 hrs	Died at 26 hrs
Present case	..	F	I	II	1,250	1,500	27.8	8.27	Slight	None	Removal of 50 ml.	Trans- fusion	Died at 7 days	A + W

A = Polycythaemic twin. B = Anaemic twin.

Discussion

In the literature available to us we found 10 other pairs of twins exhibiting the same condition. Table 2 presents the relevant data from all the cases.

The present pair is the only one in which the polycythaemic twin was the smaller of the two. The unequal distribution of blood cannot be due, therefore, to the same cause as the unequal birth weight.

It is well known that there are numerous anastomoses of all types between the placental circulations of the identical twins (Schatz, 1898). The mere demonstration by the 'milk test' of the presence of these anastomoses constituting what is called 'third circulation' (Schatz, 1898) or 'parabiotic circulation' (Klingberg *et al.*, 1955) cannot explain the unequal distribution of blood. This could arise either during labour or exist for some time before. In our case the weight of evidence is in favour of the second alternative. There were no signs of oligoemia in the anaemic twin who, furthermore, showed marked erythropoietic activity. It seems, therefore, that the blood loss must have taken place sufficiently before labour to allow for the homeostatic mechanisms to reconstitute the blood volume and to stimulate the erythropoietic tissues. For the same reason blood loss through the ruptured vessels can be ruled out as the cause of the anaemia. Moreover, this explanation cannot account for the polycythaemia of the other twin.

Seip (1956) attributed the slightly higher haemoglobin values of the second-born observed in many

pairs of twins to an additional amount of blood received from the placenta due to more complete uterine contractions. However, this explanation does not account for the great differences observed in the reported cases, in more than half of which, the polycythaemic twin was born first.

The mechanism of the unequal distribution of blood before the onset of labour is not clear. Klingberg *et al.* (1955) observed a difference in the colour and fullness of the vessels between the two parts of the placenta and believed that the more distended vessels belonged to the cord of the anaemic twin. They postulated some sort of obstruction in the venous return to the anaemic twin causing back pressure and a shunt of blood to the polycythaemic infant. We believe this to be a likely explanation but in our case we could not confirm this observation because of the rupture of the cord vessels.

Both twins are at risk but for a different reason. The anaemic infant begins its life with a low Hb content and previous authors (Klingberg *et al.*, 1955; Bergstedt, 1957; Sacks, 1959) gave blood transfusions for the correction of the anaemia. In the polycythaemic twin severe jaundice with its possible consequences is the main risk and in two cases (Bosma, 1954; Sacks, 1959) kernikterus occurred, while in two others (Bergstedt, 1957; Betke *et al.*, 1958) the serum bilirubin was above 20 mg. per 100 ml. It seems that the higher risk of kernikterus in polycythaemic newborn infants is due to the increased load of red cell breakdown

products presented to the liver cells for excretion. Klingberg *et al.* (1955) and Sacks (1959), with this risk in mind, removed blood from the polycythaemic twin.

In our case we avoided the danger facing each twin by returning to the anaemic infant the blood which was shunted to the polycythaemic before birth. Technically this procedure proved easy and it seems the best way to deal with such a situation.

Summary

A pair of uniovular twins one of which was anaemic and the other polycythaemic at birth are described. This difference was due to intrauterine transfusion of blood from one twin to the other.

The fault was corrected by removing blood from the polycythaemic twin and transfusing it to the anaemic.

We thank Professor N. Louros for permission to publish this case and Drs. M. Pavlatou and F. Fessas for help with the haematological investigations.

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Addendum

Another pair of uniovular male twins exhibiting the same condition was recently sent to us. Twin A weighing 2310 g. had Hb 23.3 g. and 7% reticulocytes. Twin B weighing 1670 g. had Hb 12.8 g. and 12% reticulocytes. When the infants were 14 hours old 40 ml. blood was taken from Twin A and given to twin B using the same technique as above; 24 hours later twin A had Hb 19.4 g. and of twin B 14.4 g. Twin A had slight jaundice never reaching dangerous levels.

PSEUDOHYPOPARATHYROIDISM IN INFANCY

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 10, 1960)

Although many of the previously reported cases of this rare condition have occurred in childhood it has not previously been diagnosed during the first year of life, despite the fact that symptoms may begin in infancy (Peterman and Garvey, 1949; MacGregor and Whitehead, 1954; Cusmano, Baker and Finby, 1956). The following report records the youngest example of pseudohypoparathyroidism yet reported.

Case Report

M.M., a coloured male infant, was first investigated in the Paediatric Section, Coronation Hospital, at the age of 3 months, for convulsions which had commenced a week before admission. There was no history of birth trauma, neonatal jaundice or epilepsy in the family. Before the onset of the fits the child had been perfectly well. Until the age of 2 months he had been breast fed and this was followed by powdered whole cow's milk reconstituted to a dilution of three parts milk to one part water with added sucrose. Lumbar puncture, skull and chest radiographs, Wassermann reaction and serum electrolytes were all normal with the exception of the serum calcium which was found to be 3.0 mEq./l. (6 mg. %). The child was diagnosed as having hypocalcaemic tetany and discharged on a maintenance dose of vitamin D (shark liver oil) 3,000 units daily.

Three weeks following discharge the fits recurred and the infant was readmitted for investigation.

Examination revealed an underweight male infant weighing 7 lb. 8 oz. in a state of continuous tetany. There was pallor of the conjunctivae and mucus membranes. There was no evidence of nuchal rigidity and the head circumference was 14.5 in. Both Chvostek and Trousseau signs were strongly positive. Examination of the heart, lungs and abdomen revealed no abnormalities. Notable features were the short stubby fingers and toes and the round contour of the face.

The mother and grandmother of the child were both of markedly short stature (4 ft. 8 in.), but neither showed any abnormalities of the digits. There was one sibling, a girl aged 3 years, who was quite normal. Blood calcium and phosphorus estimations on the three subjects were within normal limits. No other member of the family was accessible for study.

Special Investigations. Radiographs of the skull, chest and long bones revealed gross demineralization of the entire skeleton. There was no evidence of intracranial or subcutaneous calcification.

Estimations on the blood revealed a mild hypochromic anaemia (Hb 9.6 g. %); the blood urea nitrogen was 38 mg. % and the serum sodium, potassium and chlorides were within normal limits. The Wassermann reaction was negative. Protein electrophoresis of the serum revealed no abnormalities. The urine contained neither albumin nor reducing substance. Microscopic examination of a centrifuged specimen revealed nothing of note. There was no excess of amino acids on chromatographic analysis. Estimations of the 24 hour excretion of both calcium and phosphorus were extremely low, the former varying between 9 and 12 mg. daily and the latter between 180 and 400 mg. daily. The pH of the urine was acid.

The serum calcium was 3.2 mEq./l. and the plasma phosphorus was 5.2 mg. %. The alkaline phosphatase was 23 King-Armstrong units.

Fat studies of the stools revealed no evidence of malabsorption.

Progress. After obtaining a baseline of blood calcium, phosphorus and alkaline phosphatase levels the patient was treated with 5,000 units of vitamin D daily with no improvement.

Several attempts were made to perform the Ellsworth-Howard test but these were frustrated by the inability to obtain suitable urine specimens. The patient was then given 100 units of parathormone (Lilly) every eight hours for four days with no significant rise in the serum calcium level. This particular batch of hormone had produced a phosphate diuresis in the control subject for the Ellsworth-Howard test.

Throughout the entire period of observation (Fig. 1) the serum calcium remained below normal and the patient was subject to repeated attacks of tetany until treated with dihydrotachysterol (AT10 Bayer) 3 ml. daily with added calcium supplements. Thereafter the serum calcium rose steadily to normal levels which were maintained. This was associated with a fall in the plasma phosphorus.

Discussion

The diagnosis in this case rests on the failure of parathyroid hormone administered parenterally to

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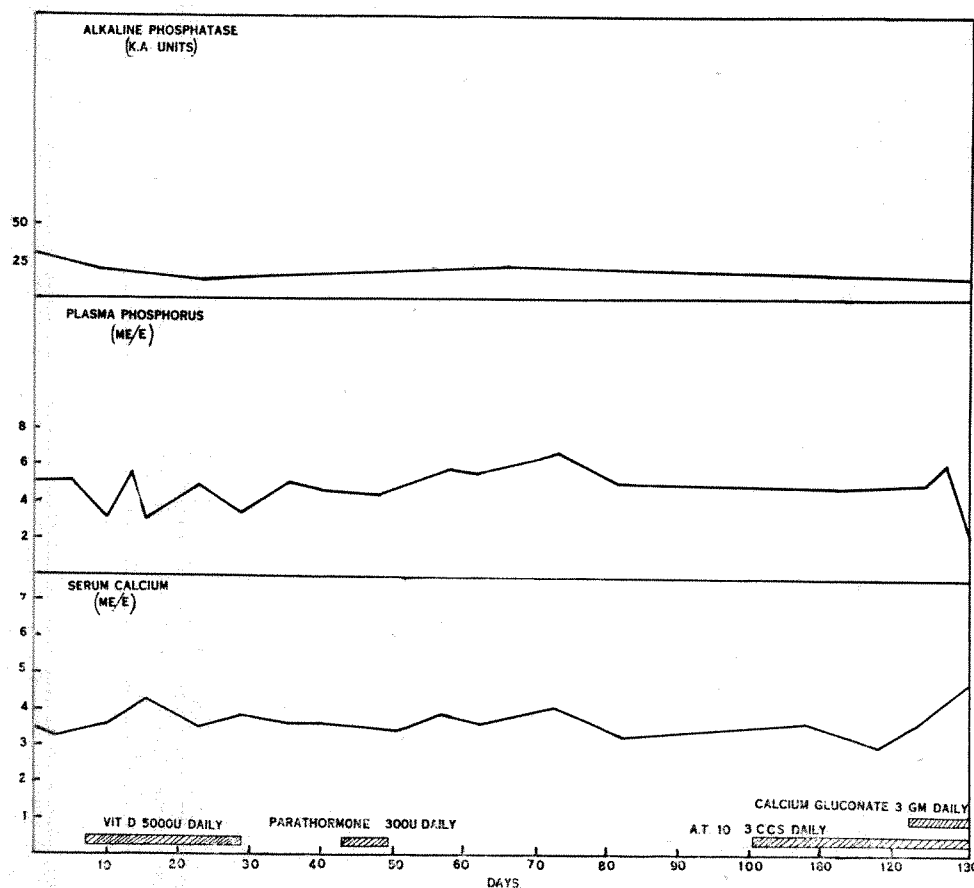


FIG. 1.—Serum calcium, plasma phosphorus and alkaline phosphatase levels and response to treatment.

produce a rise in the serum calcium with a concomitant fall in the phosphorus level. It was found impossible to collect the hourly specimens required for the Ellsworth-Howard test, the diagnostic procedure originally advocated by Albright, Burnett, Smith and Parson (1942). However, recently, workers have cast doubt on the validity of the procedure and suggest that the response of the serum calcium and phosphorus levels to parathyroid hormone over a definite period of time is a more reliable method of assessing tissue response to parathyroid (Dent, Bishop and de Mowbray, 1953; MacGregor and Whitehead, 1954; Wilkins, 1957). It is thus felt that the diagnosis in this case is valid in spite of the inability, for technical reasons, to demonstrate the classical absence of phosphorus diuresis.

Chief interest in this case lies in the youth of the patient. Many of the previously reported cases had undergone irreversible changes including cataracts,

mental deficiency and subcutaneous and intracranial calcification. Our patient was quite free of these stigmata. It seems, at least, likely that some of these sequelae might be averted if cases were diagnosed early and effective treatment instituted before changes occurred.

Of considerable interest is the presence in this patient of skeletal decalcification. Eight similar cases have been collected from the literature and it appears likely that they form a definite entity. In many of this group, demineralization of the bones with symmetrical shortening of the metacarpals is the dominant radiographic finding (Peterman and Garvey, 1949; Elrick, Albright, Bartter, Forbes and Reeves, 1950; Reynolds, Jacobson, Edmondson, Martin and Nelson, 1952; MacGregor and Whitehead, 1954; Prentice, 1954; Frame and Carter, 1955; Oberst and Tompkins, 1955; Jackson, Hoffenberg, Linder and Irwin, 1956). This, together with the low serum calcium levels suggests that there is a

generalized depletion of the total body calcium which cannot be accounted for by the accepted theory that there is a failure of tissue response to parathyroid hormone. In addition, this depletion cannot be explained by the ectopic areas of calcification. It seems likely that there is, in addition to the failure of parathyroid response, either decreased absorption of calcium from the gastrointestinal tract or excessive loss in the urine. It is known, however, that urinary loss of both calcium and phosphorus is extremely low in these cases. Furthermore, nephrolithiasis has not been described as a complication. One must conclude therefore that calcium absorption is impaired. It is also of interest that some cases of pseudo-hypoparathyroidism require additional calcium supplements as well as AT10 or massive doses of calciferol in order to raise the serum calcium to normal levels. The present patient shows this feature. Despite the fact that he was receiving three times the recommended adult dose, it was only when oral calcium gluconate was added to the regimen that the serum calcium responded. That this defect is not due to vitamin D deficiency is indicated by the raised plasma phosphorus in these cases and the normal alkaline phosphatase. It seems possible that there is, in these patients, a selective block to the absorption of calcium from the gastro-intestinal tract. It is suggested that this might take the form of an additional enzyme defect in the intestinal mucosa, resulting in the defective absorption of calcium. The exact nature and existence of this defect can only be elucidated by calcium balance studies.

Summary

Pseudohypoparathyroidism is described in a 4-month-old infant.

The presence of generalized decalcification of the skeleton is noted and eight similar cases collected from the literature.

It is suggested that in addition to the failure of tissue response to parathyroid hormone there is an additional enzyme defect present, manifesting as an impairment of absorption of calcium from the gastro-intestinal tract.

I wish to thank Dr. Harold Falcke and Dr. Harvey Cohen, Paediatricians at Coronation Hospital, and Dr. O. Elliot, Superintendent at Coronation Hospital, for permission to publish this case and the Photographic section, Department of Medicine, University of the Witwatersrand for the Figure.

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SUBSerosal HAEMATOMA OF THE ILEUM

BY

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Angiomas of the ileum are rare. Their association with a duplication cyst has not so far been described. The unusual mode of presentation, with intestinal obstruction and a palpable mass (subserosal haematoma) simulating intussusception, have prompted the report of the present case.

Case Report

N.C., a white male infant, born June 18, 1958, was admitted to hospital on May 18, 1959, when 11 months old, with a five days' history of being irritable and apparently suffering from severe colicky abdominal pain for the previous 24 hours. On the day of admission his bowels had not moved and he vomited several times.

He looked pale and ill and a mass could be felt in the right hypochondrium. There was no significant abdominal distension and the bowel sounds were within normal limits. A saline enema was given which showed a small amount of mucus but no blood. A diagnosis of intussusception was made, and after resuscitation with intravenous therapy the same evening laparotomy was performed, which showed no evidence of intussusception, but instead a large subserosal haematoma, involving approximately 7 cm. of ileum, 30 cm. from the ileo-caecal junction, and which formed the tumour that had been felt clinically (Figs. 1 and 2). In the middle of the haematoma there was a hard yellow small tumour; the mesenteric glands were slightly enlarged and some were blueish in colour. Resection of the diseased segment with end-to-end anastomosis was performed, and the appendix was removed.

The child remained ill for a few days but recovered and was discharged home on the seventh postoperative day, when he was taking feeds well and gaining weight.

When last seen, two months after operation, he was thriving and no further appointment was considered necessary.

The appendix, as expected, showed no macro- or microscopic abnormality; the mesenteric gland showed, on microscopic examination, only sinus catarrh. The resected gut, on macroscopic examination, showed a segment of intestine 9 cm. long, half way along which there was a haemorrhage over an area of 4 cm., which had lifted the serosa from the rest of the wall. On the outer aspect, also half way, there was a small diverticulum 1 cm. long, which, however, did not appear to

communicate with the lumen of the small bowel. Opposite, the mucosa had a small erosion'.

Microscopical examination (Figs. 3, 4 and 5) showed that 'considerable haemorrhage had occurred in the serous, muscular and mucous coats. The mucosa, however, was viable and the maximal zone of damage was towards the serosa. Numerous large capillaries were present in the coats. The lining of the diverticulum formed by glandular epithelium suggesting ileal mucosa was partly destroyed, but it had a well-formed muscular coat': it was considered to be probably a duplication. The main diagnosis was that of haemangioma of the ileum.

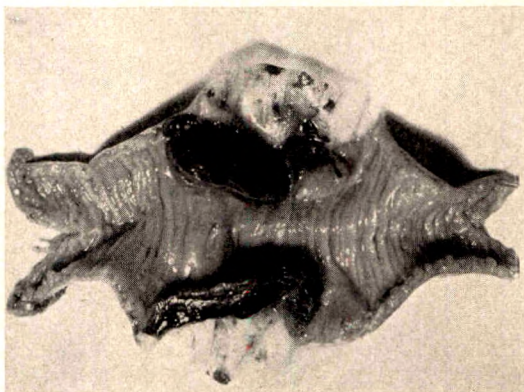


FIG. 1.—Resected specimen showing subserosal haematoma and narrowing of the intestinal lumen as well as a small mucosal erosion at the level of the duplication.

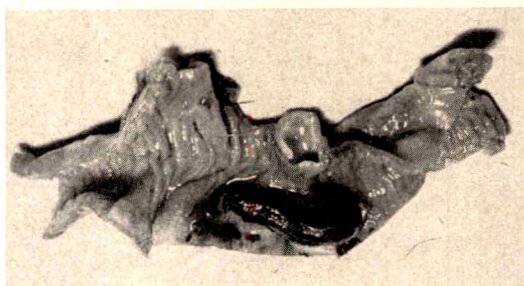


FIG. 2.—Resected specimen showing duplication cyst.

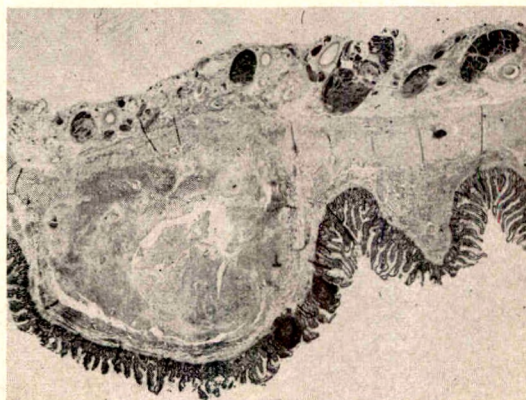


FIG. 3.—Low power magnification showing numerous vascular spaces in the subserosal area and a large area of haemorrhage in the submucosa.



FIG. 4.—Low power magnification of the duplication cyst and the common muscular wall with the intestine.

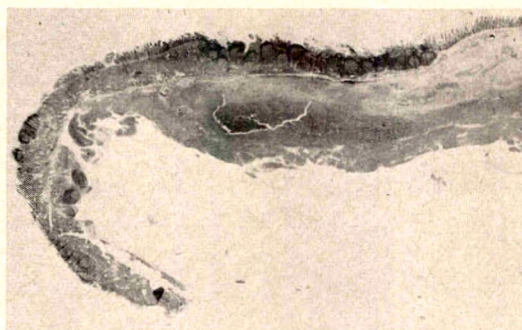


FIG. 5.—Lower power magnification in the main zone of haematoma formation, with haemorrhagic infiltration of all the bowel wall.

Discussion

As haemangiomas are common in children it is surprising to find how rarely they involve the gastrointestinal tract. The great majority of cases have been reported in adult life. According to Hansen

(1948) only 66 haemangiomas of the small bowel have been reported in the literature, and of these, only two were malignant (Ewing, 1940). Raiford (1932) quoted by Rickham (1952) found, in a series of 11,500 autopsies, that haemangiomas of the small bowel constituted 0.3% of all tumours of the gastrointestinal tract.

They can be diffuse infiltrating lesions with resultant thickening of the wall and narrowing of the lumen, or localized tumours projecting into the lumen. They are sometimes multiple and may be associated with haemangiomas elsewhere.

Simple capillary and/or cavernous haemangioma of the small bowel present frequently with gastrointestinal bleeding and occasionally are the leading point of an intussusception. More rarely they can lead to intestinal obstruction, due to the size of the tumour itself.

We think the case reported here is the first case described which presented by a subserosal haematoma. The differentiation from an intussusception was obviously impossible clinically. Treatment, however, was not influenced by the diagnosis as laparotomy was indicated in both cases.

Subserosal haematomas leading to intestinal obstruction have been reported by Zabin (1952), Lampert, Goodfellow and Wachowski (1954), and Robbarts (1957), but in those cases the children were older, with a definite history of non-penetrating abdominal injury, and examination of the resected specimens did not show haemangiomas. They were usually found near the more fixed zones of the gut, mainly near the duodenojejunal flexure.

The finding of a tumour in the centre of the area of haematoma made us look for some relationship between them, but without success. The tumour was small, smooth, rounded and yellowish, with a well-defined muscular wall in part common to the gut wall. It was cystic, with no communication with the intestinal lumen, and must be considered as a small duplication cyst. Although it is true to say that no agreed theory has so far been presented to explain the formation of those intestinal duplications, it seems certain that embryologically the haemangioma and the duplication have different origins and must be considered as coincidental but unrelated findings. Duplications of the gut, although not frequent, are a well known entity to the paediatric surgeon: Gross (1953) describes 71 cases, of which 19 were in the ileum. In the Alder Hey series Basu (1959) found seven in the ileum, out of a total of 29.

Although intramural haemorrhage in association with duplication of the intestine has been described

we could not find, in our case, evidence of the bleeding being due to the duplication.

The treatment of subserosal haematoma is resection, particularly when associated with any other bowel lesion, e.g. tumour, duplication. In the traumatic cases also we favour resection and feel that the simple evacuation of the blood clot, although successfully used by Lampert *et al.* (1954) and Robbarts (1957) should only be employed in exceptional circumstances when resection is too risky or contra-indicated.

Summary

A case of haemangioma of the ileum in an 11-month-old boy, presenting with subserosal haematoma leading to marked narrowing of the lumen and to intestinal obstruction, and showing a clinical picture typical of intussusception, is reported.

A small duplication of the ileum was found at the same level and considered to be a coincidental but unrelated finding.

My thanks are due to Miss Isabella Forshall for allowing me to publish this case; to Drs. Edward G. Hall and Jean Bouton for the pathological report, and to Mr. Charles Fitzsimons for the microphotographs.

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A CASE OF WOOLLY HAIR NAEVUS

BY

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This rare anomaly of the hair was first described by Wise (1927) and since then has received little attention in dermatological textbooks and literature. Wise reported on 'a peculiar form of birth mark of the hair of the scalp, hitherto undescribed, with a report of two cases'. He named the condition woolly hair naevus.

The disorder occurred in two unrelated 5-year-old girls, both of whom had light woolly hair on one portion of the scalp while the rest of the hair was straight and brown. One had a linear naevus of the skin of the back of the neck, right elbow and wrist, on the same side as the woolly hair on the scalp. In advancing his reason for the designation given to the condition, Wise stated that birthmarks of the hair are changes in the 'colour, consistency, structure and morphology of the hair shaft'.

Wise and Sulzberger (1932) described a similar scalp anomaly in two cases of 'acquired progressive kinking of the scalp hair accompanied by changes in its pigmentation'. The patients were adult males with kinky black hair growing over the frontal, temporal and parietal areas of the scalp which progressed rapidly when it developed. The condition appeared in adult life and the hair became darker in contrast to Wise's earlier cases which were children and in which the hair was of a lighter colour than that of the remainder of the scalp.

There was a lapse of 16 years before any further reports appeared in the literature. Anderson (1943) presented a case to the Los Angeles Dermatological Society. The patient was a 5-year-old girl and the lesion had been present since birth and had been gradually increasing in size. The naevus was on the left side of the scalp and consisted of an irregular, oval area in which the hair was lighter and closely kinked. The scalp in the affected area was of a café au lait colour which extended down in a streak on the left side of the neck. In the discussion on the case it was stated that the condition was apparently a naevus of an unusual type, showing woolly hair quite different from the hair on the other parts of the scalp.

Switzer (1948) presented a case to the Minnesota Dermatological Society which he called woolly hair naevus. The case was that of a 4-year-old girl who had a scanty growth of hair with a fine kinky texture. In this case the hair had been shed at the age of 5½ months and replaced by a scanty down; there had been no further growth since the child was 2 years old. There was no evidence of any inflammation of the scalp nor was there any evidence of naevi elsewhere. In the discussion of this case it was stated that in the original cases the condition was characterized by localized areas of woolly hair among normal hair, while in this case it was a generalized condition. There was a suggestion of an ectodermal defect in the quality of hair and, therefore, it did not seem that this was a genuine example of woolly hair naevus.

Since these reports four other cases have been described. Hoffmann (1953) described a case in which there was a considerable amount of seborrhoea of the woolly hair portion of the scalp. This case, first seen at the age of 4 years in 1917, had areas of bright, thin, spiral crinkled hair. The microscopic appearance of the affected hair showed it to be thinner than normal, more flat and less pigmented. The medullary part was more or less missing. The skin of the affected areas was browner than the skin of the remainder of the scalp and its surface was somewhat rough. Nine years after first being seen the condition was unchanged but it appeared that the affected hairs grew more slowly than the normal hairs. Hoffmann (1953) called the condition crinkly hair naevus (*naevus ulotrichicus capillitii*) and stated that differentiation must be made between crinkly hair naevus and negro hair and familial curly hair which involves the whole scalp.

Knierer (1955) described a case which resembled the condition reported by Wise and Sulzberger (1932); the patient was an adult and the hair in the affected areas was darker than elsewhere. Born (1957) and Post (1958) also reported cases which resembled those originally described by Wise.

In Post's patient, a 7-year-old boy, the woolly areas were accompanied by linear verrucous naevi on the face, neck and arm. In none of the reported cases has there been a family history of a similar abnormality.

Until now it appears that this condition has not been described in British literature and the present case is the first to be reported upon in Britain so far as is known.

Case Report

A boy, aged 6 years, was seen at the out-patient department; for about four years his hair had shown a patchy fuzziness, which was now thought to be becoming more obvious. The boy's mother stated that he had been born with no hair on the scalp and it was not until he was 2 years old that he began to develop scalp hair, which was noticed to have a peculiar patchy and fuzzy appearance, the fuzzy areas being of a lighter colour than the rest of the scalp hair. The first area to be noticed was over the back of the head and, thereafter, further areas had appeared.

During the past four years the areas had extended slightly, had remained fuzzy, and had been persistently lighter in colour than the unaffected areas. At no time was it noticed that the abnormal hairs were deficient in growth nor did they appear to be any weaker than those of the rest of the scalp.

Family History. The patient's parents were alive and well and had no hair defects or other abnormalities. The patient was the younger of two children, the elder brother being healthy with no congenital defects. The patient was a normal full-time spontaneous delivery. His maternal uncle was said to have had some defect of his hair but this was thought to have been a generalized condition. No examination could be carried out as the uncle had been in Canada for five years and had apparently now lost most of his hair. It was not considered that he had had a woolly hair naevus.

Past History. The patient's general health was excellent. He had measles at the age of 4 years and had been known to suffer from myopia for about one year, having worn glasses since that time.

Examination. The general appearance was that of a normal healthy boy, with no abnormal findings on general examination. Examination of the scalp showed normal distribution of hair with no obvious deficiency of growth. There was no seborrhoea or other scalp abnormality. The most striking feature was the presence of areas of fuzzy, lustreless hair which were noticeably lighter in colour than the rest of the scalp hair. The normal hair was dark brown and the affected hair was a much lighter brown. The involved areas were over the occipito-parietal regions on both sides, the temporo-parietal regions on the right and left and the frontal aspects of the scalp. These areas were separated by the much darker areas of straight normal hair (Fig. 1) and the affected



FIG. 1.—Woolly hair naevus.

hairs, despite their appearance, were of the same texture as the rest of the scalp and showed no increased fragility. The eyebrows were of normal appearance and there was no abnormality of the finger and toe nails or the teeth. Examination of the eyes revealed a web-like opacity over the pupil of the right eye (Fig. 2).

He was referred to the ophthalmologist whose report was as follows: 'The patient has a very extensive moderately dense membrane covering the pupillary area of the right eye. It arises from the lesser circle and, as can be readily seen, it allows free movement of the pupil. There are fine openings in the membrane and it is un-

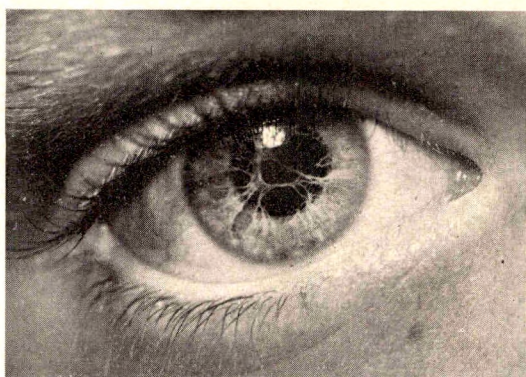


FIG. 2.—Persistent pupillary membrane.

likely that the vision in the eye is affected by it. No treatment is recommended.'

Microscopic examination of hairs from the affected and normal areas revealed no abnormality of the hairs. There was no evidence of monilethrix, trichorrhexis nodosa, pili torti, or other hair defects. The affected hairs were slightly curly and they were rather less pigmented than the normal straight ones.

Discussion

The case described is, in the writer's opinion, an example of the condition described by Wise as woolly hair naevus. There is, in common with all previously reported cases, no family history of similar naevoid changes in the scalp hair.

The diagnosis should be straightforward once the condition has been recognized. The differentiating points in distinguishing it from the condition described by Wise and Sulzberger (1932) are that it is not an acquired anomaly; it occurs in children; in all cases the affected areas are lighter in colour than the normal hair; it is not a generalized condition but a patchy one; the affected areas are interspersed by normal and darker hairs; it does not spread rapidly when it develops; and there is no microscopic abnormality of the affected hairs. Other hair abnormalities can be ruled out by the fact that in most of them there is a deficiency in hair growth and an increased fragility of the hairs which is not apparent in woolly hair naevus. Microscopic examination of the hairs will decide the diagnosis as other defects have a characteristic appearance.

Post (1958) suggested that there are three types of woolly hair naevus: (1) a type without any visible changes of the glabrous skin or scalp, (2) a type accompanied by linear naevi of the skin and (3) a type acquired in adult life in which the hair of the scalp assumes the characteristics of the pubic hair. While accepting the first two groups, the case under discussion being an example of the first, the writer feels that the third group should not be classified as a woolly hair naevus but should be classified as acquired progressive kinking of the hair as described by Wise and Sulzberger (1932).

The persistent pupillary membrane is not so rare a condition as it was once thought to be and has been reported as being found in 506 out of 1,600 eyes. It is most common in infants and children, and rare in old age as it tends to be absorbed with advancing years. Pupillary membrane remnants have the essential characteristic that if they retain contact with the iris they are always attached to the superficial mesodermal layer on its anterior surface usually at the lesser circle or occasionally more peripherally. In all cases they are extensible and do not impede movements of the pupil, or interfere with vision unless they are very dense. As regards the present case, it is felt that the presence of a mesodermal defect associated with an ectodermal one is purely coincidental and of no special significance.

Summary

The literature on woolly hair naevus is briefly reviewed and a case is described which had no associated skin or scalp changes. The patient had a persistent pupillary membrane. As far as is known, no similar case has previously been reported in Britain and this is only the seventh example so far described in world literature.

I would like to thank Dr. A. Girdwood Fergusson for his helpful criticism and for permission to publish this case, Dr. A. M. Brogan for the ophthalmic report, and Mr. P. S. Waldie for the photographs.

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CAROTID THROMBOSIS IN CHILDHOOD

BY

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(RECEIVED FOR PUBLICATION JANUARY 26, 1960)

Although carotid occlusive disease is not uncommon in adults (Fisher, 1954; Samuel, 1956), it is rare in children. Since atherosclerosis is accepted by most authors as the major aetiological agent, this is not surprising. A search of the literature reveals 16 cases of carotid occlusion in persons 10 years of age or less (Duffy, Portnoy, Mauro and Wehrle, 1957; Cabieses and Saldias, 1956; Behrman, 1954; Shapiro, 1952; King and Langworthy, 1941; Litchfield, 1938; Gross, 1945; Martin, Lukeman, Ranson and Geppert, 1954; Goldstein and Burgess, 1958; Pouyanne, Arné, Loiseau and Mouton, 1957; Clark and Linell, 1954; Braudo, 1956; Fairburn, 1957) and a further six below the age of 20 (Pouyanne *et al.*, 1957; Krayenbühl and Weber, 1944; Petit-Dutaillis, Janet, Thiébaud and Guillaumat, 1949; Riechert, 1938; Caldwell, 1936).

Arteriographic, necropsy or operative proof was provided in 17 of these cases; two were diagnosed on the absence of carotid pulsation on the side opposite the hemiplegia and three, associated with trauma, were accepted on convincing circumstantial grounds.

An aetiology was indicated in 13 cases. Litchfield (1938) and Pouyanne *et al.* (1957) have each reported a case associated with severe throat infection. Gross (1945), in a review of arterial occlusion in infancy, reported two cases in whom emboli from a thrombosed persistent ductus arteriosus were considered to have caused the occlusion. One of these cases also had Fallot's tetralogy with polycythaemia. A paradoxical embolus of necrotic placental tissue was presumed by Clark and Linell (1954) to have caused internal carotid occlusion in an infant with erythroblastosis foetalis. In the case reported by Duffy *et al.* (1957) thrombosis was probably due to a congenital anomaly of the vessel wall. Martin *et al.* (1954) have described a case of mucormycosis of the central nervous system in which the thrombosed internal carotid artery was heavily invaded by the organism. Riechert's case (1938) appears to have been related to the presence of a nearby intracranial tumour.

Trauma accounted for five cases (Braudo, 1956; Fairburn, 1957; Caldwell, 1936), direct injury to the soft palate being responsible in each instance.

In all of the proven cases the occlusion was limited to one or other internal carotid artery; one of the others (King and Langworthy, 1941) was thought to have common carotid and right subclavian obstruction on clinical grounds. Bilateral carotid involvement is occasionally encountered (Ochs, Sensenbach and Madison, 1954; Batley, 1955; Silverstein, 1959; Brain, 1957), but has never previously been reported in a child. Common carotid thrombosis constitutes a small fraction of several series of carotid occlusive cases (Silverstein, 1959; Shapiro and Peyton, 1954; Ameli and Ashby, 1949; Gurdjian and Webster, 1953) but no proven case in childhood has yet been reported. The following case of a child with bilateral common carotid thrombosis may thus be worth reporting.

Case Report

A girl of 2½ years, was admitted to the Royal Liverpool Children's Hospital for investigation, having recently recovered from an illness diagnosed as left ventricular failure associated with respiratory infection. She was known to have a precordial systolic murmur since the age of 2 months when she presented with a chest infection.

On admission there was no evidence of congestive failure and she was not dyspnoeic. Sinus rhythm was present. The left radial and femoral pulses were diminished and delayed compared with the right radial, and blood pressures were as follows: right brachial 180/130 mm. Hg, left brachial 135/85 mm. Hg, right femoral 110/90 mm. Hg. Both carotid pulses were palpable and of high tension. Scapular collateral arteries could be felt only on the right. The toes were moderately cyanosed but the fingers only slightly. The heart apex beat gave the powerful localized thrust indicative of left ventricular hypertrophy and on auscultation a short systolic bruit of slight to moderate intensity and a short mid-diastolic bruit of moderate intensity were present at the apex. The second heart sound was somewhat accentuated and single. The clinical state was otherwise within normal limits.

The chest radiograph showed a cardio-thoracic ratio

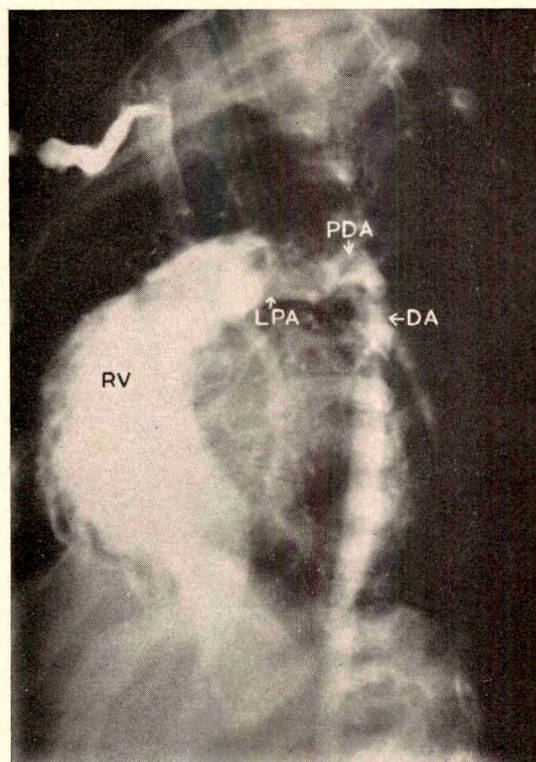


FIG. 1.—Angiocardiogram taken in right posterior oblique position, showing direct passage of dye from left pulmonary artery to descending aorta via ductus arteriosus.

RV = right ventricle; LPA = left pulmonary artery; PDA = patent ductus arteriosus; DA = descending aorta.

of 0.69 and the pulmonary vascular markings were heavy. The electrocardiogram was interpreted as showing biventricular hypertrophy. Her haemoglobin was 95%, white cell count 13,000/c.mm., differential count normal, urine normal and blood urea 25 mg./100 ml.

Two weeks after admission the patient suddenly developed left hemiparesis; this improved considerably within a few days. She had always been irritable and after this episode her temperament worsened. It was not until two weeks later that the carotid pulses were checked when neither could be felt at all.

Angiocardiography was carried out and this showed direct filling of the descending aorta from the pulmonary artery via a patent ductus arteriosus (Fig. 1). The small proportion of dye which passed through the lungs outlined only the ascending aorta and innominate artery (Fig. 2).

Three days later the right hand and forearm suddenly became cold and blue. The right brachial pulse was unaltered but the radial and ulnar pulses had disappeared. Heparin and 'Priscol' were administered and after several days the colour and temperature of the limb improved. The pulses remained unchanged. A week after the

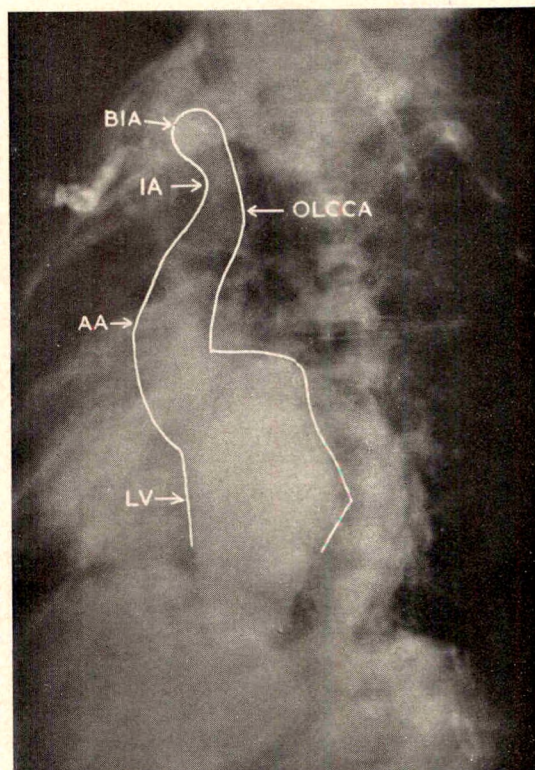


FIG. 2.—Angiocardiogram at a later stage than that shown in Fig. 1. That portion of the dye which has passed through the pulmonary circulation outlines only the left ventricle, the ascending aorta and the innominate artery. Neither carotid vessel has filled. Reference to Fig. 3 assists orientation.

LV = left ventricle; AA = ascending aorta; IA = innominate artery; BIA = region of bifurcation of innominate artery; OLCCA = region of origin of left common carotid artery.

onset of this episode the patient suddenly became unconscious and died a few hours later.

At autopsy (see Fig. 3) the heart was found to be greatly enlarged. The right ventricle was well developed and its wall up to 5 mm. thick. The left ventricle was markedly hypertrophied, its wall being up to 15 mm. thick and its endocardium white and slightly thickened. The pulmonary artery was normal in appearance but larger in size than the ascending aorta. The ductus was patent and 5 mm. in diameter. There was marked constriction of the aortic arch between the origins of the left common carotid and left subclavian arteries, admitting only a very fine probe. The left atrium was essentially normal apart from some whitening of the endocardium and slight thickening of the mitral valve cusps. The right atrium and the other three valves were normal and there was no abnormality in the anatomy of the pulmonary or systemic venous connections. Atrial and ventricular septa were intact. Adventitial haemorrhages were visible in the following sites: (a) over the root of the left common carotid artery where it was joined by the

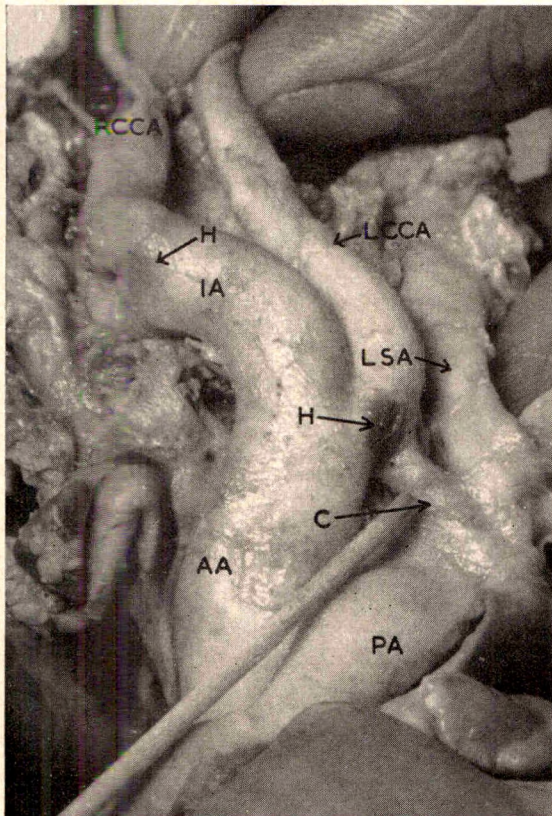


FIG. 3.—Great vessels. The right common carotid artery has been opened at its bifurcation to show the presence of thrombus. A haemorrhage can be seen in the wall of the left common carotid vessel at its junction with the coarctation; another at the bifurcation of the innominate artery is less well seen.

AA = ascending aorta; IA = innominate artery; RCCA = right common carotid artery; LCCA = left common carotid artery; LSA = left subclavian artery; C = coarcted aortic arch; PA = pulmonary artery; H = haemorrhage.

stenosed part of the aortic arch, (b) at the bifurcation of the innominate artery, and (c) at the origin of the first branch of the right subclavian artery. The last was larger than the others and had spread into the adjacent connective tissue. Antemortem thrombus was present (i) in the left common carotid artery, extending from a point 2 cm. distal to its origin to its bifurcation some 3 cm. distally, (ii) in the right common carotid artery, extending from a point 1 cm. distal to its origin to its bifurcation 2.5 cm. distally and (iii) in the right subclavian artery, commencing at the origin of the vertebral artery and extending 4 cm. distally. No origin for emboli was found in the heart or aorta. The lungs showed generalized congestion. In the brain, a small area of softening was present in the right cerebral hemisphere superior to the insula. Thrombus was present in both internal carotids at their junction with the circle of Willis, the right being swollen suggesting

antemortem thrombosis. Histology of the left common carotid artery and intracranial portions of both internal carotid arteries showed antemortem thrombus. The vessel walls showed no obvious disease.

Discussion

The case described was one of pulmonary hypertension with shunt reversal through the patent ductus arteriosus, associated with severe aortic coarctation, and complicated by multiple thromboses in the high tension side of the systemic arterial circulation.

The child appears to have lived for some weeks with occlusion of both common carotid vessels. Her ability to do so with no more than slight hemiparesis and a certain amount of irritability of temperament, was a tribute to her vertebral blood supply; her sudden death can presumably be ascribed to thrombosis of the right subclavian artery with involvement of its vertebral branch. The disturbance affecting the right forearm a few days before death, must have been caused by occlusion of the radial and ulnar arteries, or perhaps the brachial bifurcation. This could have been due to local thrombosis, or embolism from non-occluding right subclavian thrombus.

The cause of the vascular thrombosis is not readily apparent. No source of emboli was found at necropsy. Paradoxical emboli from a silent venous thrombosis would have had to move upstream and negotiate the coarctation in order to pass from the ductus to the carotid and right subclavian arteries: this seems unlikely.

Cross sections of thrombosed artery showed no abnormality of the vessel wall on microscopy. Certainty on this point, however, probably demands longitudinal sections as well, as shown by Moberg and Reinand (1956). They described the case of an infant with aortic coarctation proximal to a patent ductus arteriosus, in which thrombosis of the descending aorta occurred. Differential cyanosis was present as in our case, but could have been either peripheral in type, due to the thrombotic occlusion, or central, due to pulmonary hypertension and shunt reversal. Longitudinal sections of the aorta showed multiple transverse ruptures of microscopic size along its whole length, above and below the coarctation. Thrombosis probably arose at the site of minute intimal ulceration. Also, numerous haemorrhages, situated mainly in the media, were present throughout the aorta. The histology was considered to resemble that usually found in aortic dissecting aneurysms. The common association of the latter with coarctation of the aorta is well known, although rupture distal to the

stenosis is uncommon, tending usually to involve the ascending aorta.

The presence of adventitial haemorrhages at the proximal ends of the thrombosed vessels suggests that the pathogenesis might have been the same as in Moberg and Reinand's case in which there were haemorrhages in the aortic wall. Longitudinal sections, which might have shown transverse ruptures, were not made in our case.

No other cases of thrombosis of major systemic arteries complicating either coarctation of the aorta or pulmonary hypertension with reversed central shunt, have hitherto been reported.

Summary

The literature of carotid occlusive disease in childhood is briefly reviewed.

A case of multiple arterial occlusion, including bilateral common carotid thrombosis, in a child with congenital cardiovascular disease is described.

The aetiology of the thrombosis is speculatively discussed.

This case was under the care of Professor J. D. Hay and I would like to thank him for allowing me to report it. I wish also to thank Dr. J. S. Elwood for the autopsy report. They both very kindly provided the photographs.

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BOOK REVIEWS

Pediatric Dermatology. By HENRY H. PERLMAN. (Pp. xii + 477; 203 figs. \$18.00; 135s.) Chicago: The Year Book Publishers Inc. British distributors: Interscience Publishers Ltd.

Dr. Perlman, who is Clinical Professor of Pediatrics at Jefferson Medical College and Associate Professor at the University of Pennsylvania, is to be commended for his courage and industry in writing a textbook on dermatology. While he writes primarily for paediatricians, general practitioners and students, many dermatologists would find the book a useful addition to their bookshelves, for good books upon paediatric dermatology are rare. The latter would find added interest in a work based upon the principles of paediatric medicine, with a secondary approach to dermatology. The author's wide experience in two specialties and in pharmacology gives him an unusual breadth of approach which is reflected in the excellent chapters on physical examination and history-taking that few of us can hope to emulate. His wisdom in advocating the simpler and well tried remedies is a fresh current of common sense throughout the chapters on treatment and topical remedies.

There follows some thought provoking observations on the skin hygiene of the newly-born and only aesthetic objections can be raised against the idea of leaving more to nature and not approaching godliness via soap and water unless the infant has a normal skin.

Inevitably an experienced dermatologist can find a few weak spots as critical reviewers find in our own writings. We found some confusion in the account of subcutaneous induration of the new born. Whilst a low olein content of the subcutaneous fat may lead to the formation of fatty crystals of a higher melting point and a granulomatous reaction to their presence, which we regard as the specific basis of sclerema neonatorum, subcutaneous fat necrosis in infants or adults is not related to the olein content and has a banal histology. Dr. A. M. H. Gray deserved a reference here.

No mention is made of agammaglobulinaemia which has been recorded in cases of dermatitis gangraenosa and probably accounts for the infant's grave susceptibility to infection. Injections of gamma globulin may be life saving in some cases.

Although the old and little used arsenical medication is included in the treatment of dermatitis herpetiformis, the more effective drug diamino-diphenylsulphone is omitted from the schedule of treatment. A better name for granuloma pyogenicum is granuloma telangiectaticum, for whereas the abundance of vascular tissue is obvious, the pyogenic factor can rarely be demonstrated.

It is stated that aphthous stomatitis is caused by the herpes virus. Harvey Blank and others have failed to confirm this aetiology.

Surely too much stress is put upon the treatment of strawberry marks and cavernous haemangiomas, most of which may more safely be left for the usual spontaneous resolution.

Lest we damn, by faint praise, in finding minor points of disagreement, which may be controversial in any case, let us add that this is a good book; the standard of printing, illustrations and binding is of the highest. It is almost pure American with perhaps too few references to the outside world literature. However, the standard of dermatological knowledge and progress is probably the highest in the U.S.A., and it merely remains to one who has suffered the pangs of book-birth to congratulate the author.

Notes on Infant Feeding. By STANLEY GRAHAM and ROBERT A. SHANKS. (Pp. 76. 4s. 6d.) Edinburgh: E. and S. Livingstone Ltd. 1960.

A hearty welcome can be given to another edition of this little book at the very reasonable price of 4s. 6d. It contains much useful advice and information which is concisely given and it can be recommended equally to the student and young doctor. Some of it seems a little old-fashioned and the Sassenach baby, for instance, nowadays seems to double his weight well before the six months the authors allow.

Pathology of Infancy and Childhood. By AGNES R. MACGREGOR. (Pp. 631; 388 figs. 75s.) Edinburgh and London: E. & S. Livingstone Ltd. 1960.

Agnes Macgregor of international renown is one of the foremost pioneers of paediatric pathology. Her colleagues in the United Kingdom especially owe much to her influence and this book places them further in her debt. As she says in the preface it is not intended primarily for those familiar with the subject but for those pathologists who deal only occasionally with paediatric problems. As such it fills a long-felt gap in the literature.

About one third is taken up with the perinatal period and congenital malformations. The remainder is devoted to the infective, degenerative, metabolic and neoplastic diseases which occur in later infancy and childhood. There are also short but extremely valuable chapters on blood diseases, accidental injuries and poisons.

Most of these subjects are dealt with inadequately in general pathological texts, but here they are given their proper emphasis. For this reason paediatricians and paediatric surgeons will find this an extremely useful book. The pathological aspects of almost all their clinical problems are described in one volume of convenient size.

Of particular interest to the occasional paediatric pathologist are the observations on sudden unexpected

deaths, the advice on perinatal autopsy technique and the tables of normal measurements found at the end of the book.

The text is well set out in clear print and is not interrupted by unnecessary detail. Important references are given at the end of each chapter and there is a complete index at the end of the book. The illustrations are well chosen and clear and those of the cardiac malformations and the whole lung slices are of particular merit.

This book should be included in the libraries of all paediatric and pathological departments.

Le Syndrome D'Ellis-Van Creveld. Une forme de dysplasie chondro-ectodermique. By L. DAYER. (Pp. iv + 59; 18 figs., 4 tables. sFr. 12.50.) Basel and New York: S. Karger. 1960.

The author has reviewed 33 published cases of the syndrome (ectodermal dysplasia, polydactyly, chondrodysplasia and congenital morbus cordis) and has added four personal observations showing either the complete syndrome or variants, e.g. punctate epiphyseal dysplasia. Of a total of 36 cases regarded as examples of the syndrome, 11 showed parental consanguinity and 10 belonged to five sibships, including one pair of dizygotic twins. Recessive inheritance which was postulated when the three original cases were reported in the *Archives of Disease in Childhood* in 1940 appears to be confirmed. Of the 36 cases reviewed, 18 were boys and 18 girls. The condition has now been described in children of Jewish, English, Dutch, French, Italian, Swiss, Turkish, Algerian, Tunisian, Anglo-Irish, coloured American and mixed parentage. Of the various features of the syndrome, congenital morbus cordis seems to be the least constant, being present in only 20 cases, and ectodermal defects the most constant. The author points out that the syndrome is one of a number in which chondral and ectodermal dysplasias coexist, and that transitional types occur.

Child Development: An International Method Study.

Ed. A. HOTTINGER and H. BERGER. Modern Problems in Pediatrics, V. Supplement to Annales Paediatrici. (Pp. ix + 237; 20 figs. sFr. 50.-) Basel/New York: S. Karger A.G. 1960.

The reviewer is in the embarrassing position of being asked to write a testimonial for a favourite son and seven grandchildren. Nevertheless, he feels gratified at being able to commend this quite remarkable achievement of an international study which, fostered by the International Children's Centre in Paris, derived from the Child Study Centre in London, a product of collaboration between the University's Institutes of Education and Child Health. Nine chapters set out the history of the coordinated studies, the general considerations and lines of work, followed by three important sections on the

social, psychological and physical (somatic) investigations. A chapter on the special aspects of the problem in under-developed countries, and another on the effects of malnutrition on growth, takes the study out of Europe into West and East Africa. Dr. Faulkner's own, slightly different, present work in Louisville, Kentucky, marks the spread of the collaboration to the New World. An appendix of 100 pages gives some idea of the complexity of the data collected by reproducing the various forms in use. A study of these shows how necessary is the final chapter in the body of the volume on the practical problem of recording and analysing the completed schedules. Indeed the difficulties of getting corresponding growth studies started in eight centres seem small compared with the rapidly growing problem of what to do with the material collected. This is a valuable contribution to paediatric literature and an essential guide book for those embarking on growth and development studies. The whole text is in English, well presented and the volume beautifully produced. Professor Robert Detré contributes a characteristically charming foreword.

Kinderheilkunde: Diagnostik-Therapie, Prophylaxe. By ERWIN GRUNDLER and GERHARD SEIGE. (Pp. 846, 848 figures. DM. 29.-) Stuttgart: Hippokrates-Verlag. 1960.

This is a beautifully bound and printed synopsis of children's diseases, written in a telegraphic style. The synopsis includes a little on normal development, gives physiological values, describes infant feeding and the various immunizing procedures before the systematic description of the illnesses in childhood. It ends with a chapter of over 100 pages which gives an alphabetical list of all drugs used at present (and in the past), together with all the available proprietary preparations, giving doses, methods of administration, indications, mode of action and side-effects. For a synopsis the book is too voluminous. It would gain a great deal by drastic pruning of out-dated material. For example, it treats syphilis with arsenic and bismuth, advises deep x-ray therapy for hyperplasia of the thymus in infants and devotes a chapter to thymus lymphaticus. On the aetiology of infantile diarrhoea the concepts of exudative and neuropathic diathesis are still maintained and its dietary management is equally antiquated. Bed-wetting should not be treated by corporal punishment, but the example of good children should be constantly kept in front of the offender; favourite foods and other pleasures should be denied until the offenders mend their ways. One could give a long list of such quaint ideas. In summary this book includes all that is new without having discarded much from the past which is no longer tenable.

THE GENETIC MECHANISM OF GALACTOSAEMIA*

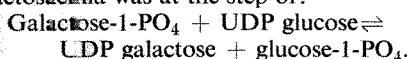
BY

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Galactosaemia is a hereditary disease of carbohydrate metabolism characterized by a failure to thrive, vomiting and jaundice in early infancy. Babies with this condition usually present with these symptoms and they are found to have enlarged firm livers, which soon become cirrhotic; this has been borne out by autopsy reports. They may be oedematous and have a tendency to bleed easily. Cataracts and mental retardation are common complications. The diagnosis can be confirmed by a markedly elevated galactose tolerance test and the finding of galactose in the urine. Schwarz, Golberg, Komrower and Holzel (1956) showed that galactose-1-phosphate accumulated in the erythrocytes of galactosaemic children if they were given galactose or milk. This indicated that galactokinase, which is the enzyme that converts galactose to galactose-1-phosphate, must be present in such individuals. In the same year, Isselbacher, Anderson, Kurahashi and Kalckar (1956) demonstrated a deficiency of galactose-1-phosphate uridyl transferase in the red blood cells of these children. This indicated that the site of the metabolic block in galactosaemia was at the step of:



It is now generally agreed that galactosaemia is transmitted by a Mendelian autosomal recessive gene. This is because of its frequent occurrence amongst siblings, its equal distribution in both sexes and the increased incidence of consanguineous matings amongst the parents of these children. Holzel and Komrower (1955) attempted to study the genetics of this condition by subjecting the parents of galactosaemic children to a galactose tolerance test. In only one family were they able to show that both parents were abnormal. In each of the four other families tested only one of the

parents gave an abnormal result; Durand and Semach (1955) found an abnormal galactose tolerance test in one parent; Bray, Isaac and Watkins (1952); Bain, Bowden, Chute, Jackson, Sass-Kortsak and Walker (1957); Schreier, Acker and Henckel (1957); and Bennett (1958) failed to demonstrate any abnormalities in the parents they tested. Hsia, Huang and Driscoll (1958) have since shown that a group of heterozygotes can be detected by estimating the blood level of galactose-1-phosphate uridyl transferase. This is discussed in more detail later.

The purpose of this paper is to present a complete family with galactosaemia and to give evidence that the disease is transmitted by a Mendelian autosomal recessive gene; it also sets out to show how enzyme studies in this family confirm the recessive mode of inheritance, that heterozygotes as a group can be detected and finally it demonstrates that galactosaemia can be present in a relatively unaffected adult.

Clinical Description of Family J

This family came to our notice from a genetic point of view as a family suffering from renal glycosuria. On investigation it was found that the reducing substance in the urine was galactose and as a result, all available members of the family have been studied. The pedigree is given in Fig. 1 and clinical details below:

- I₁ R.W., born 1894, had been thought to have diabetes mellitus for 16 years but has never needed insulin. The reducing substance in his urine has recently been shown to be galactose. Now he is in reasonably good health attending to his office business daily, and he is of above average intelligence. His eyesight is impaired because of cataracts and also he has an enlarged firm liver.
- I₂ B.W., born 1900, is healthy and has no reducing substance in her urine.
- II₁ R.W., born 1925, was known to have had a reducing substance in his urine since the age of 11 and to have a normal glucose tolerance test. He was healthy but not robust, and when put on an ulcer regime containing one or two pints of milk a day he found

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that he felt quite ill and so stopped it himself. He has five children, all of whom are well.

- II₂ A.J., born 1926, had been thought to have renal glycosuria for the past 10 years and when the diagnosis had been established in her children, it was found that the reducing substance in her urine was also galactose. She prefers to avoid milk, and has had much less intermittent diarrhoea, fewer headaches and has felt generally in better health since being on a milk-free diet.
- II₃ K.M., born 1928, has remained in reasonable health but had a reducing substance in her urine when she was pregnant. She has had one miscarriage and two healthy children.
- II₄ W.W., born 1931, was discharged from the services because a reducing substance was persistently found in his urine. Otherwise he was healthy.
- II₅ H.F., born 1935, has never been robust; she looks unwell with a rather pale translucent skin. She has had five pregnancies; two ended in miscarriages, two were premature births, the babies dying, and one a healthy child. She felt ill when pregnant, and was known to have a reducing substance in the urine at those times.
- II₆ S.C., born 1937, was in good health and has no reducing substance in her urine.
- II₁₁ J.J., born in 1920, admitted to no ill health and came from a large healthy family.
- III₁ T.J., born in 1948 at term by caesarean section because of a transverse lie, weighed 6 lb. 14½ oz. Although not particularly jaundiced at birth, he was an extremely difficult baby to feed because of vomiting. None of the usual artificial feeds suited him. In spite of his not regaining his birth weight until he was 1 month old, he was always an active baby. He smiled at 5 weeks, had some control of his head at 8 weeks, sat in a high chair at 5 months, pulled himself up to stand at 6 months, walked with

support at 11 months and by himself at 1 year. He could say single words at 15 months and talked at 22 months. Hence, there has been no evidence of any mental retardation and his subsequent progress at school has always been more than satisfactory. At about the age of 9 months, his mother took him off regular milk because she felt it did not suit him, and his condition subsequently improved. Since the age of about 1 year, he has complained of headaches and his mother correlated these with the taking of milk. He has had many unpleasant ill-defined episodes, which culminated in an alarming attack, in which he shook violently, had blurred vision, profuse sweating and almost lost consciousness. This attack had occurred after gulping a large bowl of milk and cereal at breakfast and was relieved by taking a sugar drink. At this time he was known to have a reducing substance in his urine with a normal glucose tolerance curve. It was the investigation of this presumed hypoglycaemic attack that led to the establishment of the diagnosis of galactosaemia. Examination now revealed him to be a tall, thin boy, of 9 years old, weight 65 lb., height 55 in. He has red hair and a rather translucent skin, bilateral cataracts and pale retinæ; the liver and spleen were not palpable, and there were no other abnormal physical findings. The reducing substance in his urine was shown to be galactose by its failure to ferment with yeast; this was confirmed by the osazone test. Other laboratory data are given in Table 1. Since being on a milk-free diet, he has grown 1 in. and gained 3½ lb. in six months. He has been free of headaches, has felt much better and, instead of being a rather docile apprehensive boy, he has more energy and is full of spirit; in addition, his scholastic attainments have improved. Any relaxation of his diet, however, brought back the headaches and symptoms reminiscent of the hypoglycaemic attack.

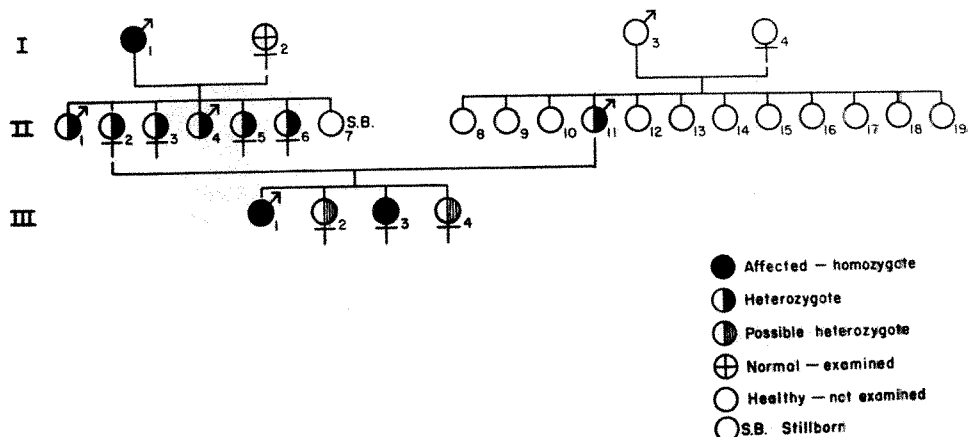


FIG. 1.—Pedigree on Family J.

TABLE 1
LABORATORY AND BRIEF CLINICAL DATA ON FAMILY J

		Gal-1-P Uridyl Transferase Level (units/g. Hb)			Galactose Level (mg./100 ml. blood)			Cataracts	I.Q.	Probable Genetic Status
		Mean	S.D.	Range	No value should be more than 50; reading should return to fasting level in 2 hrs Usually normal Values more than 50 mg.					
Values for Normals		4.13	±1.4	2.8-7.0 (16)*						
Values for Heterozygotes		2.9	±1.1	1.1-5.5 (23)*						
Values for Affected		0.6	±0.47	0-1.1 (16)*						
PEDIGREE Ref. No.	Initials	Random	Fasting	1 hr	2 hrs	Fasting	1 hr	2 hrs		
I 1	R.W.		0.9			59	115	42	+	N
I 2	B.W.	3.4								N
II 2	A.J.		1.7	1.8	1.7	8	28	6		N
II 11	J.J.		1.8	1.0	0.9	7	31	10		N
III 1	T.J.		0.6	0.6	0.4	7	86	54	+	N
III 2	M.J.		1.8	2.0	2.0	11	49	4		N
III 3	S.J.		1.0	0.8	0.5	10	45	10	+	N
III 4	B.J.		2.5	2.4	—	10	83	—		N
II 1	R.W.	1.1								
II 3	K.M.	3.4								
II 4	W.W.	2.1								
II 5	H.F.	2.5								
II 6	S.C.	4.1								

* Number of cases of which mean is recorded.

III₂ M.J. was born in 1950. Although her mother had some hypoglycaemic episodes during this pregnancy, she was born at term by caesarean section weighing 7 lb. 9 oz. She was breast fed for four months, thrived well from the beginning and has always been healthy, although she had an intussusception at the age of 4 months. She passed her milestones normally and is now a healthy intelligent girl.

III₃ S.J., born 1953, at term by caesarean section, weighing 6 lb. 14 oz. Vomited constantly from birth and had intermittent diarrhoea. When mother's milk failed she was extremely difficult to feed on cow's milk. When first admitted to the hospital at 3 months with a tentative diagnosis of congenital hypertrophic pyloric stenosis she weighed only 8 lb. Every type of milk feed was tried, but all were vomited. At 7 months of age she had a convulsion, which was thought to be related to an attack of pyelitis; at this time she only weighed 10 lb. She passed her milestones normally, sat at 6 months, walked between 10 and 11 months and was talking at the age of 2 years. She had frequent headaches, a poor appetite and 'chills' after drinking milk.

On examination she was found to be 39½ in. tall and weighed 28 lb. She, too, has red hair and a pale translucent skin unlike her two unaffected siblings. She had a palpable liver and bilateral cataracts but was otherwise normal. When the diagnosis was established in her brother T.J., her mother realized that she too was suffering from the same disease and enzyme studies confirmed this. Since then she has been on a milk-free diet, has grown 1½ in. and gained 5 lb. in six months. She has been free of headaches, felt better and done better in school though perhaps not quite so dramatically as her brother. Neither T.J. nor S.J. can

tolerate more than 1 oz. of milk on alternate days without the recurrence of symptoms.

III₄ B.J. was born in 1955, three weeks prematurely, by caesarean section because of a transverse lie. She weighed 7 lb. 11 oz. at birth and has thrived ever since. There were no feeding difficulties but a congenitally dislocated hip was diagnosed when she was 4 months old. It has been satisfactorily treated with splints and she stood at 7 months, walked at 13 months and is now a bright alert little girl.

Laboratory Data

Methods and Results. Galactose tolerance tests were done in the usual manner after an overnight fast. *D*-galactose was given orally in doses of 40 g. for adults, 1.25 g./kg. body weight for children and 1.75 g./kg. body weight for infants. A fasting blood sample, and others, one and two hours after taking the galactose, were collected in heparinized tubes and packed in ice until they were brought to the laboratory, the same samples being used both for the galactose determinations and the enzyme assays.

Blood galactose was determined by removing the glucose with glucose oxidase and estimating the remaining reducing substances by the Nelson Somogyi method.

Galactose-1-phosphate uridyl transferase was estimated by the method originally described by Anderson, Kalckar, Kurahashi and Isselbacher (1957). The method depends upon incubating a haemolysate of the red cells which contain the enzyme with known amounts of galactose-1-phosphate and uridine diphosphoglucose (UDPG). The reaction then proceeds from left to right as shown by the equation above. A unit of enzyme is that amount which will convert one micromole of UDPG to UDPGalactose in an hour. After the incubation period the remaining UDPG is estimated by means of uridine diphosphoglucose dehydrogenase in

TABLE 2
DETAILS ON PUBLISHED CASES OF GALACTOSAEMIA

Author	Case No.	Details of Families	Author	Case No.	Details of Families
Von Reuss (1908)		●	Patz (1953)	1	● ● ●
Goppert (1917)		● ● ● ●		2	●
Fanconi (1933)	+	○ ○ ○ ● ○ ○ ○ ○ ○ ● order not stated	Fox, Fyfe and Mollison (1954)		♂ ●
Boer (1932)		● ●	LoPresti, Itani and Rice (1952)		♀ ● ●
Mason and Turner (1935)		○ ○ ○ ○ ○ ●	Lockhart and Roboz (1954)		As LoPresti et al. (1952).
Norman and Fashena (1943)		○ ●	Bickel and Thursby-Pelham (1954)		● ●
Mellinkoff, Roth and MacLaggan (1945)		●	Hudson et al. (1954)	1	○ ○ ● ●
Bruck and Rapoport (1945)		●		2	♀ ♂ ● ● ●
Goldbloom and Brickman (1946)	1	○ ●		3	○ ●
	2	●	Arthurston and Meade (1954)		○ ● ○ ○ ○
Goldstein and Ennis (1948)		○ ○ ● order not stated	Cox and Pugh (1954)	1	◇ ♂ ♂ ♂ ● ◇
Greenman and Rathbun (1948)		●		2	♀ ♀ ●
Bell, Blais, Lindsay and Watson (1950)		♀ ●		3	○ ○ ●
Donnell and Lann (1951)	1	●	Hartmann, McCoy, Swarm and Nakasato (1954)		●
	2	◇ ♂ ● ●	Lodding (1954)	+	♀
DuShane and Hartmann (1951)		○ ○ ○ ○ ●	Jeune, Charrat and Loaec (1954)		♂ ♂ ♀ ♀ ♀ ● ●
Townsend, Mason and Strong (1951)	1	○ ●	Holzel and Komrower (1955)	1	♂ ● ●
	2	◇ ● ● ♀		2	●
	3	○ ○ ●		3	♂ ● ♀
	4	●		4	♂ ●
Ellenburg and Peterson (1951)		♀ ● ●		5	+
Gorter (1951)	1	○ ○ ● ●	Clay and Potter (1955)		●
	2	●	Mortensen and Sondergaard (1955)		●
McCue (1951)		●	Ritter and Cannon (1955)		●
De Haas (1951)		○ ○ ○ ○ ○ ○ ● ●	Durand and Semach (1955)		♂ ● ●
Enns (1951)		●	Rathbun (1955)		●
Falls, Lowrey and Anderson (1951)		●	Flury and Berger (1955)	+	♀ ♀ ●
Edmonds, Hennigar and Crooks (1952)		♀ ○ ○ ○ ○ ○ ○	Haas and Newman (1955)		♂
Langewisch and Bigler (1952)		●	Salt, Ross and Gerrard (1955)		●
Bray, Isaac and Watkins (1952)	1	●	Smith (1955)		♂ ♂ ♂ ◇ ●
	2	♂	Kalckar, Anderson and Isselbacher (1956)	1	♀ ● ● ●
	3	◇ ●		2	●
Brodie, J. L. (1952)		● ● ● ● ● ● ●		3	♂ ●
(1958)		As Brodie (1952)	Komrower, Schwarz, Holzel and Golberg (1956)	1	◇ ◇ ◇ ◇ ● ●
Pitt (1952)		●		2	●
Reiter and Lasky (1952)		●			
Johns (1953)		♂ ● ●	Turnbull (1956)		● ○ ●
Hsia (unpublished data) (1952)	1	♀ ♂ ●	Clément, Combes-Hamelle and Saada (1956)		○ ○ ○ ● ○ ○ ○
	2	♀ ●			order not stated
	3	●	Rodier (1957)		●
Maris and Valcke (1953)		♂ ●	Gillot, Schaeffer and Dalaut (1957)		●
Birdsong and Wood (1953)		○ ○ ●	Bain, Bowden, Chute, Jackson, Sass-Kortsak and Walker (1957)	1	●
Hartmann, Grunwaldt and James (1953)		●		2	♂ ♂ ●
Johnson (1953)	1	○ ○ ○ ○ ◇ ●		3	♂ ♂
	2	♀ ♂ ●		4	♂ ♂ ♀ ●
	3	●		5	◇ ◇ ● ●

TABLE 2 (continued)

Author	Case No.	Details of Families
Schultze-Jena and Schafer (1957)	1	◇ ♂♂♂
	2	○ ○ ♂♂♂
Schreier, Aker and Henckel (1957)		○ ○ ♀
Wilhelm (1957)		♂
Bennett (1958)		○ ♂

KEY	
Male	♂
Female	♀
Sex not recorded	○
Miscarriage or stillbirth	◇
Cataracts	⊙
Cirrhosis	⊙
Reducing substance in urine	⊙
Trace of reducing substance in urine	⊙
Abnormal galactose tolerance test	⊕
Galactosaemia	●
Consanguinity	+

the presence of DPN. The amount of haemoglobin in the haemolysate is calculated and the enzyme expressed as units per g. of Hb. Huang, Hugh-Jones and Hsia (1959) have described these methods in detail.

Using these methods the results obtained in this family are given in Table 1. Normal values for this laboratory are given at the top of the Table. The grandfather, who clinically had had a reducing substance in his urine for years (recently proven to be galactose), a large liver and cataracts, was found to have an abnor-

mal galactose tolerance test and an enzyme level within the affected range. The two of his grandchildren, who had typical histories of galactosaemia, also had enzyme levels within the affected range. The enzyme determinations on the grandfather's six children showed them, as a group, to be heterozygotes and the only one who was free of symptoms had the highest enzyme level.

Genetic Analysis of Literature

All the available published literature on galactosaemia has been reviewed. All families containing a case of galactosaemia have been tabulated (Table 2). For a case to be accepted as one of galactosaemia it must have had the typical clinical history of failure to thrive and feeding difficulties since birth, jaundice and an enlarged liver, a reducing substance in the urine after the first week of life and albuminuria. The reducing substance must have been proven to be galactose either by (1) its failure to ferment with yeast, (2) positive mucic acid test, (3) osazone crystal formation or (4) by paper chromatography. Many cases also had cataracts, were oedematous in the first week of life and had a tendency to bleed. Once a case had been diagnosed in a family others were quite often diagnosed retrospectively. These have been accepted provided they had three of the four following findings: typical history, cirrhosis, a reducing substance in the urine and cataracts. Using these criteria all the families, except those containing only one child, have been tabulated in Table 3.

Clinically, as had already been mentioned, it seems likely that galactosaemia is transmitted as a recessive gene. To confirm this the family data collected from the literature have been analysed

TABLE 3

ANALYSIS OF THE 57 SIBSHIPS WITH ONE OR MORE CASES OF GALACTOSAEMIA, COLLECTED FROM THE LITERATURE, BY THE *A PRIORI* METHOD (ONE CHILD FAMILIES OMITTED)

Family Size	No. of Families	Observed No. of Cases				Expected No. of Cases	Variance
		Male	Female	Not Stated	Total		
2	15	9	6	5	20	17.142	1.83
3	20	16	13	3	32	25.946	5.26
4	10	12	4	2	18	14.628	4.20
5	4	5	1	—	6	6.556	2.37
6	2	2	3	—	5	3.650	1.55
7	4	3	1	—	4	8.078	3.88
9	1	—	—	2	2	2.433	1.38
11	1	1	—	—	1	2.871	1.805
	57	48	28	12	88	81.304	22.275

Standard deviation = 4.72

Observed cases, excluding cases from families of size one = 88

Expected number of cases = 81

$t = \frac{\text{difference between the observed and expected number of cases}}{\text{standard deviation}} = \frac{7}{4.72} = 1.5$

7 degrees of freedom
 $p > 0.05$

by two methods. In each instance it has been shown that the observed frequency of cases was not significantly different from the theoretical incidence calculated for a recessive mode of inheritance.

In the first instance the data was analysed using the Weinberg sib method (Schultz, 1936). The formula for a recessive mode of transmission is:

$$\frac{Ta - P}{T - P} \text{ Should equal } 0.25$$

$$SE = \sqrt{\frac{pq}{T - P}}$$

Where: Ta = Total affected children in all the families
T = Total children in all the families
P = Probands
p = Expected frequency of affected
q = Expected frequency of remainder

There were 36 families with only one child, of which 18 were males, 12 females and in six the sex was unrecorded; when these were added to the data from Table 3, the formula became:

$$\frac{124 - 93}{246 - 93} = 0.2 \quad SE = \frac{0.25 \times 0.75}{153} = 0.035$$

Thus, the difference between the observed and expected value was not significant.

The data were also analysed by the 'a priori' or Apert's method. Calculating the expected number of children to be affected from Hogben's tables reproduced by Neel and Schull (1954) it will be seen from Table 3 that in these 57 families (families with only one child were omitted in these calculations) there should have been 81.3 affected children. The number observed was 88. The standard deviation is the square root of the sum of the variances. The difference between the observed and expected was 7; this divided by the standard deviation gave a 't' value of 1.5 which for 7 degrees of freedom was not significant. Therefore, the difference between the observed and expected number of affected children was again not significant.

In the total series, where the sex had been recorded, there were 66 males to 40 females. From Table 2 the sex of the unaffected siblings, where recorded, gave a ratio of 32 males to 25 females. There was obviously no significant difference between these two figures. Many of these galactosaemic children had died within the first month of life; therefore, as another comparison, the sex ratio at birth of the large Birmingham series reported by Crosse (1949) has been used. In this series of over 19,000 births there were 53% males and 47% females. This gave a calculated incidence of 56 males to 50 females for this series. Using the χ^2 test between the observed and calculated values $t = 1.92$; 1 d.f.; $p > 0.05$. So there was no statistical evidence to suggest that this difference in sex incidence was of significance. These statistical analyses confirm the clinical impression that galactosaemia is transmitted by a Mendelian autosomal recessive gene.

Discussion

As has already been mentioned, attempts to detect the heterozygous carriers of this condition

by stressing them with galactose tolerance tests have not been sufficiently precise to be successful.

During the past year three groups of workers have been able to demonstrate an abnormality amongst the heterozygous carriers of galactosaemia. Originally Hsia *et al.* (1958) reported a reduction of the enzyme galactose-1-phosphate uridyl transferase in the red cells of a group of 12 heterozygotes as compared with 11 normal controls. Bretthauer, Hansen, Donnell and Bergren (1959) modified the original method of assaying the enzyme and found that they were able to detect the heterozygous group with less overlap of the results between carriers and controls than the previous worker. Kirkman and colleagues (Kirkman and Kalckar, 1958; Kirkman and Bynum, 1959), have reported a more refined technique of enzyme assay using oxygen consumption and by this method have also shown a decrease of enzymatic activity amongst the relatives of galactosaemic individuals. The first study has been enlarged upon by the addition of further data, and also by a second attempt to detect the carrier state by measuring the accumulation of hexose-1-phosphate in the red cells under the stress of a galactose tolerance test (Huang *et al.*, 1959). The results of these enzyme assays have been analysed and are included at the top of Table 1. Although it may be difficult to evaluate the significance of the results from an individual, the difference between the enzyme levels of the normal group and the heterozygous carriers gave a value for 't' of 3.0 with 37 degrees of freedom (16 normal controls and a group of heterozygotes consisting of 18 parents and five offspring of galactosaemic patients). This difference was highly significant ($p < 0.005$). That the value for heterozygotes with one abnormal gene fell between the normals with no abnormal genes and the homozygotes with two abnormal genes lent further support to the recessive mode of transmission.

The interest in this family lay in the chance discovery of an affected adult who had affected grandchildren. From our genetic analysis of the literature we would have expected him to have two abnormal genes for galactosaemia and therefore, for him to have handed on one of the abnormal genes to each of his children. This has been elegantly confirmed by doing the enzyme levels in this family; the average enzyme level for his six children was 2.5, which was well within the heterozygous range. That one of his daughters should have married another unrelated heterozygous carrier for galactosaemia was a chance of fate, but of great academic interest. That the father of these grandchildren was a heterozygote was confirmed by the

enzyme studies. Therefore, in this family study, there was a clear confirmation of the recessive mode of inheritance and a demonstration of the laboratory techniques for detecting heterozygotes. In addition, the use of enzyme determinations was shown in confirming the clinical diagnosis.

It was not generally known that a person with galactosaemia could live to be an adult in reasonable health without treatment. One other adult case has been found by this laboratory. There were three cases in the literature reported by Ritter and Cannon (1955) and by Durand and Semach (1955), who were not diagnosed until the ages of 5, 14 and 8 years respectively. They showed little ill effects other than cataracts and no doubt could have lived normally with no more serious effects than had the grandfather I_1 R.W. Presumably his two grandchildren who were not diagnosed until the ages of 9 and 5 years could also have survived. Mason and Turner's (1935) original case is now in his late 20's but he is severely retarded.

Another unusual feature in this family was the symptomatology among the heterozygotes. II_{1-6} were all heterozygotes because their father I_1 was a homozygote. This has been confirmed by the enzyme studies. Three of his four daughters felt unwell when pregnant and had mellituria; in one II_2 , this has been proven to be galactose. His two sons had mellituria and after reducing their intake of milk their conditions improved. The only child in this family who did not have symptoms had an enzyme level at the upper end of the heterozygous range. Ellenburg and Peterson (1951) and Hudson, Ireland, Ockenden and White-Jones (1954) have reported siblings of affected cases who showed a trace of reducing substance in the urine. LoPresti, Itami and Rice (1952) and Kalckar, Anderson and Isselbacher (1956) each record a paternal grandfather who was intolerant of milk; Holzel and Komrower (1955) state that one of the fathers of their patients became ill after taking 30 g. of galactose daily. Abnormal galactose tolerance tests have been demonstrated in some parents and siblings though not regularly (Brodie, 1952; Holzel and Komrower, 1955; Durand and Semach, 1955; Komrower, Schwarz, Holzel and Golberg, 1956). This was not surprising once it was realized that the heterozygote has less enzyme available than normal and in some cases this was nearly as little as in affected individuals.

Summary

A family is presented in which the grandfather was proven to have galactosaemia by galactose tolerance tests and by the determination of the

enzyme galactose-1-phosphate uridyl transferase level in his blood. His six children were shown by similar enzyme studies to be heterozygous carriers of the condition and one of these married another unrelated heterozygous carrier and they had two affected children in their family of four. A complete review of the literature is given and genetic analysis of the data collected strongly suggests that galactosaemia is transmitted as a Mendelian autosomal recessive gene. The results of our laboratory studies in the detection of the heterozygous carrier in galactosaemia are given and these confirm, in this family, this mode of transmission.

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THE OXYGEN TENSION OF THE BLOOD IN THE UMBILICAL CORD AND THE INTERVILLOUS SPACE

BY

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During recent years there has been a revival of the interest in oxygen saturation in the umbilical blood; this work was started in the 1930's by Haselhorst and Stromberger (1931) and several papers have been published by different groups (Walker and Turnbull, 1953; MacKinney, Ehrlich, Goldberg and Cantwell, 1955; Rooth and Sjöstedt, 1955, 1957; Bancroft-Livingston and Neill, 1957; Turnbull and Baird, 1957). It should be remembered, however, that measurements of oxygen saturation mainly give an indication of the amount of oxygen present in the blood. For a more complete picture of the oxygenation it is also necessary to know the oxygen tension (pO_2) since that is the force by which oxygen is pressed from the vessels into the tissues and because the physiological effect of the oxygen depends solely on its pO_2 .

As oxygen in foetal circulation is obtained from maternal blood in the intervillous space of the placenta, a comparison between the levels of pO_2 in the intervillous space and in the umbilical vessels will indicate the diffusion pressure drop of the oxygen between the maternal and foetal circulation in the placenta.

Material and Methods

The cord blood was investigated in 178 cases after spontaneous delivery in vertex presentation. One hundred and twenty-eight of the infants were normal without any signs of asphyxia; 30 infants had signs of mild asphyxia, usually with slow or irregular heart beats. Nineteen infants had meconium stained amniotic fluid without any other signs of asphyxia.

During labour the mothers were given 'trilene' or nitrous oxide and in some cases a few drops of chloroform at the moment of delivery.

The cord was clamped immediately after birth and blood was drawn from the vein and the arteries into heparinized syringes. The analyses of the blood were started immediately.

The blood in the intervillous space was investigated in 25 cases of normal pregnancy. The placenta was

punctured through the abdominal wall before labour had started. Only local anaesthesia was used and no complications occurred. Before puncture the placenta was localized as carefully as possible by palpation and auscultation (Norman, 1953) or sometimes by radiographs. The puncture was always made below the umbilicus on the side of the legs of the foetus. When the placenta was punctured, it was an easy matter to get 10-20 ml. of maternal blood into a heparinized syringe; if the uterine wall only was punctured the outcome was a few millilitres of blood obtained with difficulty. Punctures of the human placenta have also been made by Walker and Turnbull (1959) and Prystowsky (1959).

The pO_2 was measured polarographically with the Clark electrode as described by us (Rooth, Sjöstedt and Caligara, 1959). Within the range of pO_2 observed here, the error of the analyses should be less than ± 1 mm. Hg.

Great care was taken in order to obtain as reliable information as possible about the time of gestation. Most of the mothers were under observation by the staff during pregnancy and any case in which the duration of pregnancy was doubtful was rejected from the investigation.

Results

The pO_2 values from the vein are given in Fig. 1 and from the arteries in Fig. 2. In normal cases two-thirds of the observations from the vein are between 25 and 35 mm. Hg; in the arteries two-thirds of the values are between 10 and 20 mm. Hg. The mean pO_2 in normal cases is 29.3 in the vein and 18.3 mm. Hg in the arteries.

Figs. 1 and 2 also give the pO_2 values for the asphyxiated infants and infants with meconium stained amniotic fluid. The mean pO_2 in the vein of the asphyxiated infants is 27.0 and in the arteries 16.0 mm. Hg. The mean pO_2 in the vein of the infants with meconium stained amniotic fluid is 29.2 and in the arteries 15.6 mm. Hg.

In Table 1 the pO_2 in 113 specimens from the umbilical vein and 89 samples from the arteries are divided according to gestation time. The

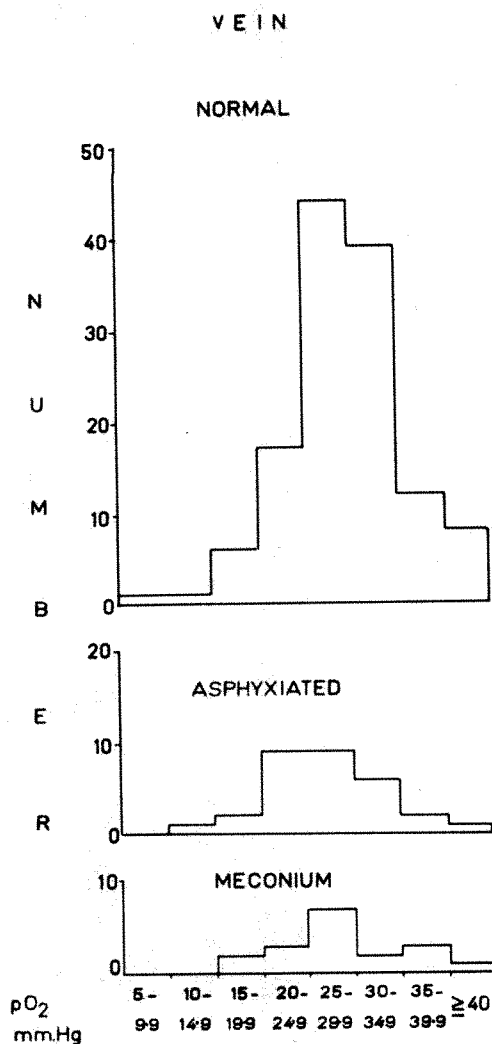


FIG. 1.—Distribution of the oxygen tension in the umbilical vein in normal and asphyxiated infants and infants with meconium stained amniotic fluid.

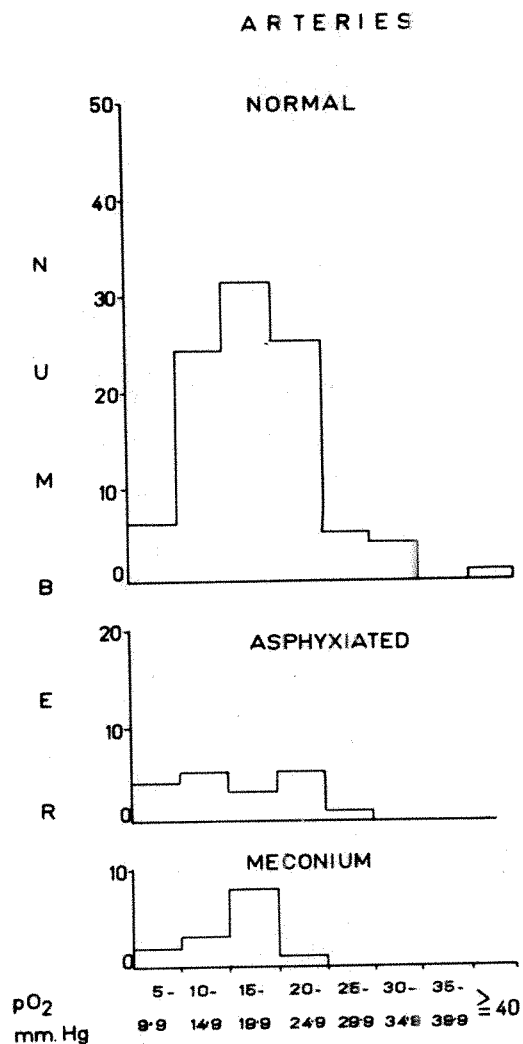


FIG. 2.—Distribution of the oxygen tension in the umbilical arteries in normal and asphyxiated infants and infants with meconium stained amniotic fluid.

differences between the different weeks are small and irregular in the whole group as well as in the primigravidae (Table 2).

The results of the analyses of the intervillous blood are shown in Fig. 3. The mean pO_2 is 39.9 mm. Hg with the range 27.5 to 53.7 mm. Hg.

Discussion

The figures available in the literature on the pO_2 of the cord blood are summarized in Table 3. Direct measurements have been made by Beer,

Bartels and Raczkowski (1955), Wulf (1958) and Sjöstedt, Rooth and Caligara (1960). Beer *et al.* (1955) and Wulf used the potentiometric method of Bartels (1951). The mean values of Beer *et al.* are lower than might be expected from the oxygen saturation analyses cited above. They are difficult to explain and may be due to the individual cases. On the other hand the values given by Wulf correspond to ours and to the majority of the oxygen saturation measurements in the literature and it may therefore be assumed that the mean pO_2 in the umbilical vein in normal cases is about 30 mm. Hg

TABLE 1

OXYGEN TENSION IN THE UMBILICAL CORD BLOOD AFTER NORMAL DELIVERY AT DIFFERENT GESTATION WEEKS

Gestation (weeks)	Vein		Artery		Arterio-venous Difference
	Number	Mean pO ₂ (mm. Hg)	Number	Mean pO ₂ (mm. Hg)	
38	4	31.8	3	21.8	10.0
39	18	28.5	12	19.9	8.6
40	36	28.5	30	18.0	10.5
41	25	31.2	18	17.5	13.7
42	18	29.6	15	19.3	10.3
43	12	28.2	11	16.0	12.2
Total	133	29.3	89	18.2	11.1

at the time of delivery and the corresponding value in the arteries is about 18 mm. Hg.

Wulf shows, as expected, that the pO₂ in the cord blood is less in the asphyxiated cases. In the present series the mean difference between the normal cases and both the asphyxiated group and the meconium group is small, but as shown in Figs. 1 and 2 there are more low values in the two latter groups than in the normal cases. In the normal

TABLE 2

OXYGEN TENSION IN THE UMBILICAL CORD BLOOD OF PRIMIGRAVIDAE AFTER NORMAL DELIVERY IN DIFFERENT GESTATION WEEKS

Gestation (weeks)	Vein		Artery	
	Number	Mean pO ₂ (mm. Hg)	Number	Mean pO ₂ (mm. Hg)
38	2	30.8	2	9.1
39	13	29.2	10	20.9
40	17	28.0	14	17.6
41	6	30.8	6	20.6
42	8	33.7	7	25.2
43	8	29.2	6	18.2
Total	54	29.7	45	19.9

cases there are 19% with a pO₂ in the vein of less than 25 mm. Hg, while in the meconium group there are 32% and in the asphyxiated group 40%. The corresponding frequency of values less than 15 mm. Hg in the arteries is 31, 36 and 50%.

Just as was found in our study on the oxygen saturation in the cord blood (Rooth and Sjöstedt, 1955), the group labelled 'asphyxiated' contains some cases with normal and others with lowered pO₂. This is explained by the fact that most of our cases of asphyxia only manifested themselves temporarily in the form of foetal bradycardia before birth.

In comparing the values between the normal and the asphyxiated cases it can be seen that the differences are much smaller for the pO₂ than they are for the oxygen saturation. This is because of

the shape of the oxygen dissociation curve. In measurements of adult arterial blood the oxygen saturation may vary from between 92 to 96%, whereas at the same time the pO₂ changes from 70 to 95 mm. Hg. This is because the values lie in the horizontal range of the oxygen dissociation

TABLE 3

SURVEY OF UMBILICAL CORD BLOOD pO₂ STUDIES

Author	Artery		Vein	
	Number	Mean pO ₂	Number	Mean pO ₂
<i>Normal pregnancy and non-asphyxiated infants</i>				
Haselhorst and Stromberger, 1931	...	...	4	31.0
Beer <i>et al.</i> , 1955	22	9.2	24	22.4
Wulf, 1958	36	15.7	36	32.0
Sjöstedt <i>et al.</i> , 1960	51	16.9	68	28.9
Present investigation	96	18.3	128	29.3
<i>Asphyxiated infants</i>				
Wulf, 1958	20	4.0	20	7.3
Present investigation	32	15.8	49	27.9

curve. With the umbilical blood the opposite occurs. The values are now in the range of the vertical part of the dissociation curve and although the oxygen saturation changes from 70 to 45% the tension only decreases from 30 to 25 mm. Hg. In this way the already initially low pO₂ is maintained, although the oxygen supply is reduced. This has been called the buffering effect of the curve (Barron, 1959).

Most obstetricians associate the presence of meconium staining of the amniotic fluid with intra-uterine hypoxia. The present series substantiates this in so far as the pO₂ in the cord blood is low more often in the meconium group than in the normal.

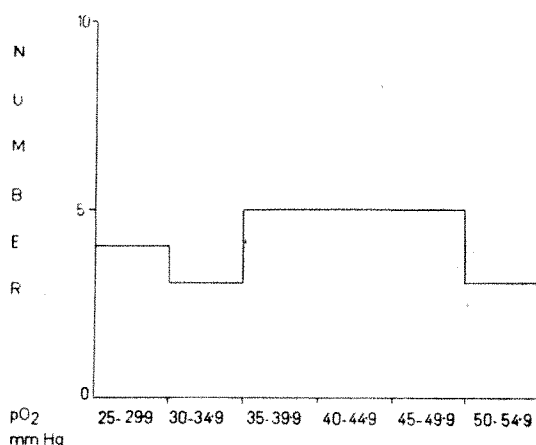


FIG. 3.—Distribution of the oxygen tension in the intervillous blood of the placenta.

According to Walker and Turnbull (1953) advancing gestation time especially after 40 weeks causes a decrease in the oxygen saturation in the cord blood. These results have been confirmed by MacKay (1957), whereas no such change has been observed by MacKinney *et al.* (1955), Bancroft-Livingston and Neill (1957) or Rooth and Sjöstedt (1957). Recently Turnbull and Baird (1957) and Walker and Turnbull (1959) have stated that this decrease only occurs in primigravidae.

In his series Wulf had nine cases of prolonged pregnancy and found the average pO_2 in the vein to be 13.3 and in the arteries 9.4 mm. Hg. Since not less than five of these infants were asphyxiated at birth and needed artificial respiration it cannot be concluded from Wulf's data that prolonged pregnancy *per se* decreases the pO_2 of the cord blood. In our series of 113 normal infants 45 cases have a gestation time of 41 weeks or more and, as shown in Tables 1 and 2, the pO_2 in the umbilical vein and arteries is about the same from the 38th to the 43rd week of pregnancy. The same is valid for primigravidae. Thus it is not possible to demonstrate any physiological change in the pO_2 in the umbilical blood immediately before, during or after term.

Nearly all authors have found the arteriovenous difference to be 10-13 mm. Hg (Table 1). Only Wulf has a bigger difference, 16 mm. Hg.

No direct measurement of the intervillous pO_2 has been published, but our mean value, 40 mm. Hg, may be compared to that of Prystowsky (1957). Prystowsky measured the oxygen saturation and estimated the pO_2 from an oxygen dissociation curve without giving any measurements of pH. In eight cases he had a mean of 37.5 mm. Hg with the range 24.0-72.0 mm. Hg. Walker and Turnbull (1959) also measured the oxygen saturation in the intervillous blood and estimated the pO_2 to be 36-40 mm. Hg. Beer *et al.* (1955) calculated the intervillous pO_2 as 30.2 mm. Hg, basing their figures on their measurements of the cord blood and data on the maternal arterial blood. As their cord blood figures were much lower than ours, as already discussed, it is not surprising to find their figure for the intervillous blood lower than ours.

It seems therefore that the normal foetus gets its oxygen supply from the maternal side of the placenta at a tension of about 40 mm. Hg. It is not yet known whether the observed scatter of ± 13 mm. Hg is due to individual variations in the mother or to fortuitous sampling near or distal to the arterial blood entering the intervillous space.

Given the data on the pO_2 of the intervillous

blood, umbilical vein and umbilical artery blood it is possible to calculate the mean drop in oxygen pressure between the maternal and foetal circulation, which is defined as the pressure drop between the intervillous space and the mean between the umbilical artery and umbilical vein. We thus find a value of 16 mm. Hg. It should be remembered that in no instance have we measured the individual pressure drop and the figure given here is one based on average normal intervillous blood and average normal foetal blood. Prystowsky (1957), obtaining the cord blood one minute after obtaining the intervillous samples, has been able in three cases to estimate the pressure drop from measurements of the oxygen saturation and found 17.7, 18.3 and 20.4 mm. Hg, i.e. figures of the same order as in our measurements. When the mothers were given oxygen, Prystowsky (1959) found that the mean pressure drop increased to 37.5 mm. Hg. Beer *et al.*, who, as mentioned, have measured pO_2 in the cord blood, made ingenious calculations of the intervillous space blood. If their figures are used in the same way to calculate the mean pressure drop it will be 14.4 mm. Hg. From this it seems that the normal pressure drop is somewhere between 15 and 20 mm. Hg. It is noteworthy that this is much higher than the corresponding drop in the alveoli, where it is of the order of a few mm. Hg. One reason for this, besides the obvious anatomical differences, is that when the blood is very hypoxic, as is that of the cord arteries, a long contact time is necessary for complete equilibration, and probably the time in question is too short in the placenta. It is extremely risky to estimate the pressure drop in the tissue between the maternal and foetal circulation in the placenta from the present figures, but at any rate it cannot be higher than the difference between the intervillous blood and the umbilical vein, i.e. 10 mm. Hg. Probably the drop is lower.

Summary

The oxygen tension in the umbilical vein at the time of delivery in normal cases ranges from 6 to 46 mm. Hg with a mean of 29.3 mm. Hg. In the umbilical arteries the range is from 6 to 32 mm. Hg with a mean of 18.3 mm. Hg.

The mean values in a group of slightly asphyxiated infants in both arteries and vein is a few mm. Hg lower.

The mean value in the umbilical vein is the same in the normal group as in a group of infants with meconium stained amniotic fluid, but the mean value in the arteries in this group is about the same as in the asphyxiated group.

In the intervillous space the mean pO_2 in 25 cases is 39.9 mm. Hg.

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ABSENT UMBILICAL ARTERY*

A REVIEW OF 113 CASES

BY

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The umbilical cord normally contains two arteries and one vein embedded within Wharton's jelly which is, in turn, enclosed by an epithelial membrane.

Hyrtil (1870) described the absence of one of the umbilical arteries in 12 instances (four infants and eight placentae) of which only two infants were malformed, one suffering from spina bifida and both having cleft palates. He also noted that male infants were affected more often than female infants and that females lacking one umbilical artery were more frequently malformed and often anencephalic. Neither the observation of male dominance nor the higher incidence of abnormalities in females have subsequently been confirmed, although there is a high incidence of anencephalic deformity in the female infants. He collected a total of 58 cases from the literature to add to the 12 of his own.

Browne (1925) reported a premature infant in whom the umbilical cord contained a single artery and the umbilical vein was replaced by a capillary network. Javert and Barton (1952) reported the results of the examination of 1,000 abortuses in which histological sections from 104 umbilical cords were examined. Only one was found to contain a single artery.

Benirschke and Brown (1955) described a retrospective study of 55 infants in whom one artery was missing from the entire length of the umbilical cord. Of these 55 only 13 (24%) were considered to be normal children and of the remaining 42 there were 27 (64%) who suffered from a wide range of congenital abnormalities, many of whom had multiple defects. Placental abnormalities were common (39%). Little (1958) examined the umbilical cords of 1,200 consecutive deliveries, finding

that 12 (1%) contained only one artery throughout, and in four (0.3%) the arteries fused locally near the placenta; congenital abnormalities were present in 25%. Recently Benirschke and Bourne (1960) reported the incidence of absent umbilical artery to be 15 (1%) in 1,500 consecutive deliveries. Eight (53%) were considered to be developmentally normal, although one was stillborn, whilst seven (47%) were found to possess major or minor congenital abnormalities. Only 12 (80%) remain alive, one of whom has survived operative treatment for oesophageal atresia and tracheo-oesophageal fistula.

It seems fairly certain that the overall incidence of this abnormality is in the region of 1% of all deliveries. Furthermore, they report that absent umbilical artery occurred seven times (7%) in a series of 100 consecutive unselected twin pregnancies. This is much higher than has hitherto been supposed.

Materials and Method

A total of 113 infants in whom one umbilical artery was absent (Fig. 1) has been studied at the Boston Lying-in Hospital and the Children's Medical Centre, Boston, Mass. The series is composed of 55 cases first observed in a mainly retrospective study, 15 cases reported to be present in the examination of 1,500 consecutive placentae, together with a further 43 instances observed during the past three years in the Pathology Department of the Boston Lying-in Hospital. With the exception of some of the 55 instances which were retrospective, the examination consisted of a gross evaluation of the placenta together with a microscopic study of at least three blocks of tissue. These included sections from the middle portion of the umbilical cord, a segment of rolled membrane and a section of full thickness placental tissue. In the event of absence of an umbilical artery from the histological section of the cord, the secundines, which had been

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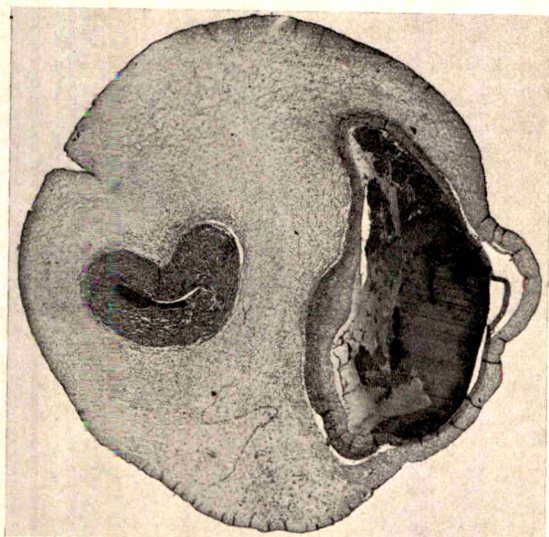


FIG. 1.—Absence of one umbilical artery. Section of the umbilical cord showing the dilated vein and a single artery. Note the muscular wall and small lumen of the artery. There are no residual ducts or vessels present. (H. and E. $\times 10$.)

stored awaiting 'histological clearance', were re-examined to confirm the absence of an artery from the entire length of the cord. In instances of foetal death confirmation of the absence of one of the intra-abdominal vessels was sought at necropsy. Owing to the high incidence of associated congenital abnormalities, it was the usual practice to inform the paediatrician immediately upon the finding of a single umbilical artery. This assisted in the early diagnosis of oesophageal atresia in at least one infant.

A total of approximately 6,000 deliveries occur each year in the Boston Lying-in Hospital. With the exception of the consecutive series mentioned above the placentae are examined in the laboratory only when indicated by such conditions as maternal illness or disease; foetal distress, abnormality or prematurity; plural pregnancy; hydramnios and other complications of pregnancy as well as patients of clinical or pathological interest.

It is realized that 98 of the total 113 cases are derived from selected material from which it might be erroneous to draw definite and final conclusions. The reasons for the selection of the material from which these cases are derived, however, are so diverse that there is ample justification for the analysis of certain factors.

Maternal Factors

Age. An analysis of the ages of the 113 mothers who were delivered of infants lacking one umbilical

artery is shown in Table 1. It is noticeable that 26 (62%) of the 42 primigravidae were under the age of 25, whereas only 13 (22%) of the 59 multigravidae were under the same age. Compared with the average ages of a control series of patients, this series shows an increased incidence of the anomaly among the younger primigravidae and the older multigravidae. The age groups of the total series, however, conform fairly closely to those of the controls, because the increased incidence at the younger end of the primigravidae scale balances the similar, but less well marked, rise at the older end of the multigravidae scale. These findings are in broad agreement with Baird and Walker (1959), who state 'The incidence of foetal deformity . . . is highest in the 15-19 age group and decreases with age till thirty-five; a slight rise occurs in the age group 35 and over'.

The average age of the 19 mothers of infants with central nervous system anomalies, 28.3 years compared with 28.5 years, failed to confirm that these, in particular, occur in a high age group (Hegnauer, 1951).

Parity. Forty-two of the mothers were primigravidae and 59 were multigravidae whose parity varied from one to 15. These are shown in detail in Table 2 and agree essentially with the control series except for the high number pregnant for the

TABLE 1
ANALYSIS OF AGES OF MOTHERS DELIVERED OF INFANTS LACKING ONE UMBILICAL ARTERY

Age (years)	Primigravida	Multigravida	Total
20	5	1	6
21-25	21	12	33
26-30	8	15	23
31-35	6	17	23
36-40	2	12	14
41	—	2	2
Total ..	42	59	101
Average age ..	25.3	30.7	28.5

TABLE 2
GRAVIDITY

Gravidity	No.
1	42
2	21
3	15
4	11
5	3
6	5
7	1
8	2
15	1
Total ..	101

sixth time, an observation that is not considered to have any significance.

The 59 women who had been pregnant previously had produced a total of 111 live born infants, 12 stillbirths (a rate of 103 per 1,000) and 32 abortions. Four of the 111 live born infants died in the newborn period so that only 107 (69%) infants survived the newborn period out of a total of 155 previous pregnancies. This incidence (31%) of foetal loss in the past history of these patients is surprisingly high and much greater than the 11% of the control series.

Maternal Diseases. A high incidence of pre-eclampsia (30%) was described by Benirschke and Brown (1955). This was not confirmed by Little (1958). Both authors agree that the large number of pre-eclamptic patients in Benirschke's series was the result of material selection and that it did not reflect the true incidence of this complication of pregnancy. This series of 113 cases includes the 55 described by Benirschke, together with a further 58 additional cases in which pre-eclampsia was diagnosed in only five (9%) instances. This indicates that pre-eclampsia is not associated with the absence of an umbilical artery either as an aetiological factor or as a result of the abnormality. Altogether a total of 19 patients (16%) were found to be suffering from pre-eclampsia in the total of 113.

The association, however, of pre-eclampsia and a single artery in a total of 19 patients resulted in seven stillbirths, three neonatal deaths and nine living infants, which illustrates that this combination, even if it is fortuitous, is particularly lethal to the foetus.

A careful study of the general health of the mothers has not disclosed any factor that might influence the pregnancy so as to predispose the foetus to this particular anomaly. The high incidence of foetal wastage in the previous pregnancies of multigravida has been described; a high proportion (8%) of patients suffered from antepartum haemorrhage.

Two otherwise normal infants suffered from erythroblastosis foetalis due to rhesus incompatibility, one being stillborn and the other dying on the first day. Four of the mothers suffered from epilepsy (*grand mal*).

Hydramnios. The incidence of foetal abnormality is particularly high in association with hydramnios. Macafee (1950) stated that the incidence of foetal abnormality was 46% in a series of hydramniotic pregnancies. It is not surprising, therefore, that there should be a fairly high incidence of hydramnios in association with absence of an

umbilical artery. Nineteen (19%) patients were considered to suffer from hydramnios in the 101 in whom adequate information was available and this figure is probably a conservative estimation, because in the original study of 55 cases only four were present, 15 occurring in the last 58 patients. This high incidence of hydramnios was not confirmed by Little (1958). It is interesting that all 19 (100%) of these infants suffered from congenital abnormalities and that 12 were stillborn; five died in the neonatal period and the two who survive do so because of successful surgical treatment of oesophageal atresia. The association between hydramnios and oesophageal atresia is now accepted (Scott and Wilson, 1957), and in one of the surviving patients the early diagnosis of oesophageal atresia was hastened by the finding of umbilical artery aplasia within a few hours of the birth of the infant.

Heredity. There is little or no evidence to show that this condition is of an hereditary nature. Only one mother was known to suffer from any major congenital abnormality (pulmonary stenosis) and one had congenital syphilis. No abnormalities were known to be present in the male parents but they were, necessarily, not subjected to the same scrutiny as the mother. Furthermore, the wide range of associated congenital abnormalities seems to mitigate against a single hereditary factor. Four mothers (4%) suffered from *grand mal*, which might be significant, but the numbers are too small to justify the assumption that it was in any way a causative factor.

There is, however, some evidence that the anomaly forms part of a diathesis in which abnormalities are frequently multiple and may be recurrent. These assumptions are based upon the past history of 59 multigravid patients in which 48 (31%) out of a total 155 pregnancies failed to produce a living child. It is unfortunate that more detail was not available concerning the loss of these infants, but such information as is available does not reveal any definite recurrence of single umbilical artery abnormality, although several are known to have produced abnormal infants previously. Several mothers have subsequently produced normal children, all of whom possessed two umbilical arteries. That these patients experience a greater than average difficulty in producing living normal children is definite and it is possible that the finding of arterial abnormalities in the umbilical cord may lead to the recognition of such 'high-risk' patients even in their first pregnancy. The parents of one infant were known to be related cousins; there was no other recorded evidence of consanguinity.

TABLE 3
DETAILS OF 15 (1%) AFFECTED INFANTS FROM 1500 CONSECUTIVE DELIVERIES

Number	Sex	Twins	Gestational Age (weeks)	Complication of Pregnancy	Foetal Anomalies	Follow-up
1	M	—	35	Chorioamnionitis	None found	Not traced
2	F	—	39	Placental infarct	None found	Normal
3	F	F/F monochorial	38	None	Forked xyphoid	Normal development
4	M	—	42	Irregular heart 0-130; discharge meconium	None found	Normal
5	M	M/M monochorial	38	650 g. lighter than other twin	Hydrocele, abnormal cardiac rhythm	Developing normally; bigger than twin
6	M	—	38	None	Slight club foot—right	Normal development
7	F	—	40	None	None found	Normal
8	F	F/M dichorial	38	None	Hyperteiorism, short fingers	No problem
9	F	—	37	Hydramnios	Oesophageal atresia and fistula, sacral anomaly	Operated, survived
10	F	—	37	Hydramnios	Anencephaly	Stillborn
11	F	—	40	None	None found	Normal
12	F	—	40	None	None found	Normal
13	M	—	37	None	Renal agenesis, atresia anl, accessory pan- creas, equinovarus	Died
14	F	—	37	Maternal floor infarct- tion; long cord	None found	Stillborn
15	F	—	40	Long cord	None found	Not traced

(After Benirschke and Bourne, 1960.)

The Infants

Incidence. In the examination of a series of 1,500 consecutive placentae a total of 15 (1%) of the umbilical cords were found to contain only one artery throughout their length. Seven (46%) of these 15 infants suffered from congenital abnormalities, of which three were of major significance (Table 3). One was a stillborn anencephalic and one died from renal agenesis. There were eight (53%) normally developed infants of which one was a macerated stillbirth in whom no congenital abnormality could be found.

The overall mortality in this short series is three out of 15 (20%) with one further child surviving operative repair of an oesophageal fistula and atresia.

The relatively high incidence of twin infants in this consecutive series (20%) is confirmed to some extent by the fact that in a series of 100 consecutive twin deliveries an absent umbilical artery was present seven (7%) times. The overall incidence of one in 100 is confirmed by Little (1958) and by Bourne (1961) who recognized the condition five times in 475 (one in 95) consecutive umbilical cords. A similar incidence is also reported by Emig (personal communication).

The Fate of the Infants. It is realized that the total series of 113 cases is partially selected, but nevertheless an analysis of these patients is very informative. Table 4 shows the fate of these infants.

Live Infants. Only 48 (42%) are alive, of whom 14 (29%) are known to suffer from congenital

TABLE 4
FATE OF THE INFANTS

Infants	Nos.	%
Total	113	100
Alive	48	42
Normal infants	34	
Known congenital abnormality	14	
Dead	65	58
Congenital anomaly incompatible with life	39	
Congenital anomaly compatible with life in infants dead of other causes	5	
Possible anomaly in unexamined infants	15	
No anomaly	6	

abnormalities; 27 infants were either seen or were considered by their medical attendant to be both physically and mentally normal. It was impossible to trace seven infants, all of whom, according to their records, were normal when last examined. In the absence of any information to the contrary these infants are considered to be living and normal.

It has been possible to trace all 14 infants who are alive and who suffer from congenital abnormalities of varying severity. Several of these infants (Table 5) are not expected to reach adult life and two survive only because of successful surgical repair of oesophageal atresia.

Dead Infants. Sixty-five (58%) of the infants died or were born dead, of whom 59 (91%) were suffering from definite or probable congenital abnormalities (Table 4), and only six (9%), who died of known causes, were considered to be normally developed for their maturity.

TABLE 5
KNOWN ABNORMALITY COMPATIBLE WITH LIFE IN 14 SURVIVORS

Maturity (weeks)	Weight (lb.)	Sex	Abnormality	Follow-up (years)	Remarks
40	7.1	F	Congenital heart disease	17	Twin
41	5.1	M	Oesophageal atresia	6	Successful operation
36	7.1	M	Brain cysts	4	Very poor prognosis
37	5.11	M	Hydrocele, umbilical hernia, inguinal hernia	4	
32	3.6	M	Mental defect; optic fundi abnormal	3	Poor prognosis
42	4.15	F	Multiple haemangiomas	2	
42	6.2	M	Arthrogryphosis multiplex cystica, cryptorchid	2	
32	2.5	M	Cryptorchid	2	Twin
39	8.0	F	Marfan's syndrome: arachnodactyle	1	
38	5.13	M	Sternal abnormality	1	Twin
38	3.2	M	Cardiomegaly (?) cause	1	Twin
38	5.8	M	Talipes equinovarus	0.6	
38	5.1	F	Hyperteiorism	0.5	Twin
36	4.6	F	Oesophageal atresia	0.5	Successful operation

Congenital abnormality of such a major degree as to be incompatible with life was present in 39 (60%) of these children, whilst five (8%) who died from other causes were suffering from anomalies that probably contributed to their death, and 15 (22%) were considered to be suffering from a congenital abnormality, although severe maceration or lack of a post mortem examination prevented exact diagnosis.

Absence of one umbilical artery seems, in itself, to be a simple and innocuous congenital abnormality, but it is associated with a perinatal mortality involving 58% of the affected infants, together with a further 12% who are alive but abnormal in some way. Such a relationship is considered to be significant.

Congenital Abnormalities. The types of congenital abnormality from which the affected infants suffered have been classified into systems. These are listed in Table 6 and they are detailed in Table 7.

The majority of the babies suffered from multiple defects which, if serious, are listed separately so that the total is greater than the number of infants concerned. No system or peculiar abnormality is particularly prominent, although aplastic lesions of

TABLE 6
CONGENITAL ABNORMALITIES

Abnormalities	Nos.	%
Known congenital abnormalities (mostly multiple)	58	51
Gastro-intestinal	31	
Skeletal	28	
Genito-urinary	27	
Cardiovascular	21	
Neurological	19	
Others	10	
Possible abnormality (unexamined, dead)	15	14
No known abnormality	40	35
Total number of cases	113	100

TABLE 7
DETAILS OF CONGENITAL ABNORMALITIES

Abnormality	Nos.
Gastro-intestinal	31
Oesophageal atresia	8
Imperforate anus	6
Exomphalos	5
Malrotation of gut	4
Herniae	4
Cleft palate	3
Cysts of larynx	1
Skeletal	28
Talipes equinovarus	9
Poly and syndactyle	6
Spine (excluding spina bifida)	5
Phocomelia	2
Arthrogryphosis	2
Achondroplasia	1
Arachnodactyle	1
Congenital dislocation hip	1
Microphthalmia	1
Genito-urinary	27
Sexual aplasia	5
Renal aplasia	5
Polycystic kidneys	4
Undescended testes	3
Megaloureters	3
Hypospadias	2
Cryptorchid	2
Recto-vaginal fistula	1
Clitoral hyperplasia	1
Double uterus	1
Cardiovascular	21
Interventricular defect	5
'Congenital heart disease'	5
Fallot tetralogy	4
Triloculare	3
Cardiomegaly	2
Coarctation of aorta	1
Absent valves	1
Neurological	19
Anencephaly	5
Hydrocephaly	4
Spina bifida	4
Mental defect	2
Angioma	1
Brain cysts	1
Cyclops	1
Nerve paralysis	1
Others	10
Turner's syndrome	2
Hyperteiorism	1
Haemangiomas	1
Pulmonary aplasia	1
Splenomegaly	1
Asplenia	1
Abnormal optic fundi	1
Cystic pancreas	1
Cystic liver	1

TABLE 8
INFANTS DEAD OF ABNORMALITIES INCOMPATIBLE
WITH LIFE

Abnormality	Stillborn	Neo-natal Death	Total
Anencephaly	5	—	5
Hydrocephaly	2	2	4
Exomphalos	1	1	2
Congenital heart disease	4	11	15
Cyclops	1	—	1
Cranial nerve paralysis	—	1	1
Spina bifida	—	4	4
Renal aplasia	1	2	3
Gastro-intestinal aplasia	—	4	4
Total	14	25	39

TABLE 9
KNOWN ABNORMALITIES IN INFANTS DEAD
OF OTHER CAUSES

Cause of Death	Abnormality
Broncho-pneumonia	Syndactyle
Hyaline membrane	Tracheo-oesophageal fistula
Stillborn macerated	Unilateral renal hypoplasia
Stillborn macerated	Cleft palate
Stillborn macerated	Talipes equinovarus

the alimentary and genito-urinary tracts are more frequent, and lesions of the central nervous system less frequent than might be expected.

Thirty-nine infants died of congenital abnormalities incompatible with life (Table 8). Congenital heart disease is the most common abnormality considered incompatible with life. Table 9 shows the anomalies present in those five infants whose death was considered to be due mainly to other reasons.

The congenital abnormalities from which the surviving infants suffer together with their weight and maturity at birth, sex, period of follow-up and comments are shown in Table 5. Several of these children will not survive to reach adult life. Eight (57%) were premature by weight although only two (14%) were born before the 36th week of gestation. This is not surprising if the absence of an umbilical artery slows the actual growth of a foetus *in utero*, but it does not necessarily prevent the foetus from maturing. It is upon maturation rather than actual body weight that the infant subsequently depends for its survival.

Trivial abnormalities such as cutaneous naevi and minor haemangiomas have not been included in this series. The number of uncomplicated or single malformations is very low. There are only 14 (24%) whilst the number of multiple abnormalities, 44 (76%) is much higher than expected. The great increase in the incidence of congenital abnormalities in this series is due mainly, but not entirely, to a rise in the number of multiple abnormalities. Neel

(1958) found that only 14.9% of malformed children had multiple defects; Schull (1958) reported that the percentage of infants with multiple abnormalities rose to 34.3% if the parents were related.

Sex. It was suggested by Hyrtl (1870) that there is a male preponderance associated with this abnormality. This was not supported by Benirschke and Brown (1955) or Little (1958), nor is it supported in the present series, which contains 55 female and 49 male infants. There is one hermaphrodite and the sex of eight infants is not recorded. An analysis of the various abnormalities, the stillbirths, surviving infants or maturity also fails to show any sex domination (other than those which are expected, such as the anencephalic infants, all five of whom were female). There is, in this series, a total of 16 twin infants, whose sex is predominantly female. There are, in fact, 13 female and three male infants. No reason is offered for this apparent female dominance, which despite the small number of cases, does appear to be significant.

Side of Absence. It is only possible to define the absent side at necropsy. Unfortunately adequate information is available upon only 22 infants in whom the artery was absent, 12 times on the right side and 10 times on the left. The intra-abdominal part of the umbilical artery was easily recognizable in more than half the babies, although in some it existed as a very thin threadlike structure. Fig. 2 demonstrates absence of the right artery. The dissection displays the branches of the aorta as seen from the dorsal aspect and shows marked aplasia of all the aortic branches on the right side. A similar developmental abnormality of these vessels was frequently noted at necropsy, but the corresponding lower limb was never smaller than the contralateral limb. When present, deformities of the lower limbs were usually more severe upon the affected side.

Maturity and Weight. The maturity of 109 infants is known out of a total of 113. Six were non-viable, i.e. born before the 28th week of pregnancy, and 103 were viable. Table 10 shows the maturity, sex, average birth weight and average placental weight of the infants. The average birth weight is lower than normal, especially in the more mature age groups. The average placental weight is also less than normal. It seems reasonable to suppose that the absence of an umbilical artery could cause a diminution of oxygen supply to the foetus and this theory receives some support from the small average foetal weight. There is, however, no compensating enlargement of the placenta.

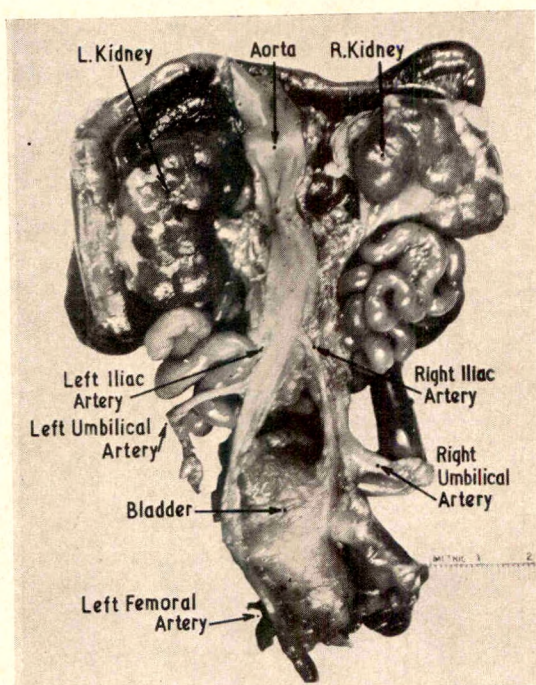


FIG. 2.—The viscera of a stillborn infant dissected and photographed from the dorsal aspect. The aorta is normal. The left iliac, umbilical and femoral arteries are normal. The right common iliac artery, which is about one quarter of its normal size, is distributed mainly along its internal iliac branches. The right umbilical and femoral arteries have no visible lumen and exist as threads in connective tissue.

Infants suffering from congenital abnormalities tend to be born prematurely and in this series 56 (59%) of the 95 viable infants of known weight were premature by weight at birth.

TABLE 10
MATURITY, SEX AND AVERAGE BIRTH WEIGHT OF
INFANTS WITH AVERAGE PLACENTAL WEIGHTS

Maturity (weeks)	Number	Sex (if known)		Average Birth Weight		Average Placental Weight (oz.)
		M	F	lb.	oz.	
<28	6	2	1	—	—	—
28	2	1	1	1	8	8
29	2		1	1	4	10
30	2	1	1	2	15	12
31	1	—	1	2	12	9
32	5	2	3	2	12	13
33	4	2	2	3	11	14
34	3	2	1	2	14	12
35	12	5	7	3	13	15
36	9	5	3	5	4	18
37	11	5	6	5	2	14
38	11	6	5	6	5	15
39	7	3	4	6	13	17
40	20	8	12	6	5	22
41	6	3	2	6	7	19
42	6	3	3	5	12	14
>42	2	—	2	5	0	17
Not known	4					
Total ..	113	48	55			

Placentae. A relatively high incidence of placental abnormality was recorded by Benirschke and Brown (1955), and Little (1958) reported an increased frequency of velamentous insertion of the umbilical cord. In this series there was a total of 32 (29%) placentae that showed gross abnormality including, velamentous insertion of the cord (12); circum-margination (five); circumvallation (five); lobed (four); placenta praevia (three) and maternal floor infarct (three). Massive infarction of the maternal surface of the placenta with resulting intra-uterine asphyxia has been noted by Benirschke and Bourne (1960) to occur in successive pregnancies and to be associated with absence of an umbilical artery.

Accidental ante-partum haemorrhage occurred in six pregnancies from which only one infant survived; four were stillborn and one died after 24 hours. Placenta praevia was present on three occasions. A history of threatened abortion was given by eight patients, an episode which did not appear to affect adversely the infant's chance of survival.

Twins. The incidence of absent umbilical artery is greatly increased in plural pregnancy. In the present series of 113 babies the abnormality occurred 16 times (14%) in twin pregnancies; only five (31%) of these 16 infants are alive and well.

In a consecutive series of 100 twin pregnancies the abnormality was present on seven occasions. This incidence of 7% of twin pregnancies, or 3.5% of twin infants, as compared with an overall incidence of 1% appears to be a significant increase. A similar unexplained observation (Stevenson, Worcester and Rice, 1950) is the finding of a doubled incidence of foetal malformation in twin pregnancies.

Benirschke and Bourne (1960) considered that the increase of this anomaly might be caused by a relatively higher proportion of monozygous twins. This appeared to be correct in a smaller number, but the present larger series of 16 infants does not support the theory. Six (37%) infants were monozygous because of monochorial placentation, while 10 (63%) were dizygous because of dichorial placentation or heterosexual twins, so that they obey the general rule regarding the zygosity of twins, which states that nearly one-third are monozygous and two-thirds dizygous.

Discussion

Variations in the number of vessels in the umbilical cord are known to occur, but the available information upon their origin and significance is sparse. The

most important vascular aberration is absence of one of the two umbilical arteries through the length of the umbilical cord and is associated with atresia of the corresponding intra-abdominal portion of the artery. This abnormality is present in 1% of pregnancies and in 7% of twin pregnancies. Anastomoses between the umbilical arteries normally occur at the placental end of the umbilical cord either in the cord itself or in the adjacent placenta. These anastomoses presumably serve to equate the intra-arterial pressures and ensure equal distribution of blood throughout the placenta. They may also act as an arterial shunt when a portion of the foetal placental circulation is closed for physiological or pathological reasons and could, therefore, exert a profound influence upon the ability of the foetus to maintain its placental reserve or to resist the anoxic effects of large placental infarcts.

Foetal Abnormalities. The incidence of congenital abnormality amongst an average population is between 1% and 2.5% of all live and stillbirths (Malpas, 1937; Logan, 1951; Lewis, 1956) of which approximately half are gross foetal abnormalities. Absence of one umbilical artery appears to be the commonest major congenital abnormality of the human foetus.

There is a significant rise in the incidence of congenital abnormalities associated with foetuses having only one umbilical artery. The width of the range of the congenital abnormalities suggests that the absence of an umbilical artery is not a secondary effect but is probably a primary lesion to which, some at least, of the associated anomalies are secondary.

It is possible that these abnormalities are the result of the hypoxia to which the foetus is subjected during the organo-genetic period. The efficiency of a single artery or the date of closure of a second artery, are not standard so that both the time and degree of relative oxygen lack would vary widely. There is no suggestion that all the anomalies in this series are caused by a single agent, as some are considered to be hereditary (Potter, 1952) but, if a factor such as anoxia were playing a part in their production, it would have to be capable of acting over a long period in order to account for the wide variety of abnormalities concerned.

However, the majority of anencephalic infants possess two normal umbilical arteries, which indicates that either absence of an umbilical artery has no teratogenetic influence, or, if it does, that there are other agents which are equally effective. Similar arguments can be forwarded concerning the other abnormalities of this series, in that they also are

considered to occur in the presence of two normal umbilical arteries so that the precise embryological and developmental significance of absence of one umbilical artery is unknown.

The high incidence of associated foetal abnormality occurring in babies with only one umbilical artery suggests that the 'anomalies' are in some way connected. The presence of only one artery in the umbilical cord may constitute a severe impediment to normal foetal development by causing a resistance to the blood flow and possible lack of oxygen to the foetus. This, together with an absence of the juxta-placental umbilical arterial anastomosis, may also be a cause of intra-uterine death. This series includes 16 twin infants and the fact that 14 (88%) of these infants were smaller than their normal siblings does support the theory that a single umbilical artery impairs normal growth.

Minor congenital abnormalities are conspicuous by their absence in this series. When two factors that are known to be associated with major congenital abnormalities are combined, such as hydramnios and absent umbilical artery, the foetal loss is particularly high.

Cardiac Malformation. There are several reasons why a high incidence of cardiac abnormalities might be associated with absent umbilical artery. In itself the absence is an anomaly of the cardiovascular system and other changes may occur because the artery normally develops during the period of rapid formation of the circulatory system. A heavy strain would certainly be imposed upon the heart if a functioning artery underwent degeneration in early foetal life. It has been shown that a single artery can support an apparently normal foetus but the resistance to blood flow and degree of cardiac overload must, at times, be considerable and may predispose to abnormalities within the heart. One might assume that measuring the diameter of the remaining artery would offer some means by which one could determine if an increased resistance to blood flow had existed in intra-uterine life. Unfortunately, the thick muscular wall causes their lumina to vary greatly after delivery, so that there is no reliable method whereby their functional efficiency within the uterus can be assessed (Reynolds, 1952).

Aetiology. It is disappointing that even such a large series does not give any definite indication of the cause of this abnormality. There is no definite evidence that the condition is familial or recurrent, although it does occur in the children of women who have a poor reproductive ability. It is more

frequent in the younger primigravida and the older multigravida. The fact that four mothers suffered from epilepsy is interesting but the number is too small to be significant.

We have considered the possibility that the vessel which was formed in a normal manner has subsequently ceased to function, and atrophied. Such a cessation of function would cause some anoxia, however transient, which could easily disturb the embryological development of the foetus and cause congenital abnormalities. The time at which the artery ceased to function would be the teratogenetic termination period and as such would determine which foetal organs would be most severely affected. If the time varied widely, so would the malformation.

The theory that the artery once was present and functioning is supported to some extent by the invariable presence of an intra-abdominal umbilical artery, albeit often attenuated, on the affected side. It is, however, difficult to accept that a properly functioning umbilical artery could entirely disappear from the umbilical cord without leaving some histological evidence of its presence. In four instances, however, the residual arterial structure was present and, having a diameter much greater than that of the vitelline vessels, it is assumed that these remnants are aplastic umbilical arteries.

It is our opinion that the second umbilical artery was never satisfactorily formed within the umbilical cord in the majority of the infants in this series but, that in a few instances, a functioning vessel was present at some stage of foetal development.

Clinical Importance. Absence of an umbilical artery, occurring in 1% of patients, is associated with a high incidence of foetal abnormality (65%). Many of these abnormalities are not obvious, nor are they readily apparent upon simple general examination of the newborn. In most maternity units the placenta, membranes and umbilical cord are examined, weighed and measured and it would be a simple procedure to examine routinely the cut end of the cord. The vessels are easily identified and the finding of a single artery should stimulate a further and more detailed examination of the infant. Such an observation might be of great benefit if the presence of unsuspected abnormality were to be considered in those cases of single umbilical artery encountered. Benirschke and Bourne (1960) report that the diagnosis of oesophageal atresia was made six hours after delivery in an infant who was re-examined following the reported finding of a single umbilical artery. The child is well one year after surgical treatment for the condition. The importance of hydramnios in association with absent

umbilical artery is stressed, for, in this series, all of the 19 infants in whom this combination was present suffered from a major congenital abnormality.

Prognosis. Details of the congenital abnormalities suffered by the affected children have been recorded together with the prognosis both before and after delivery. Absence of one umbilical artery does in itself diminish a child's chance of survival. The incidence of intra-uterine asphyxia, stillbirth and prematurity is higher than normal. The anomaly appears to cause a slowing of intra-uterine growth so that the average birth weight is less than the expected normal average. It is interesting to note that these infants, when healthy, are similar to twin infants in this respect because their ability to survive depends more upon their maturity than weight. This series produces further confirmation that this principle applies also to the single pregnancies.

When the infants are born alive their prognosis is identical to that of their associated abnormality, if present, together with superimposed prematurity. As stated above, they withstand prematurity fairly well and, having survived the newborn period, they develop physically and mentally into normal children, provided, of course, that they are not encumbered by the frequently associated congenital abnormalities.

Summary

A total of 113 cases of absence of one umbilical artery are presented and analysed, together with a review of the literature.

The abnormality is slightly increased amongst the younger primigravidae and the older multigravidae, but does not increase in incidence as parity rises. A total of 59 multiparous women had had 155 previous pregnancies from which only 107 (69%) infants survived. A total foetal loss of 48 (31%) is considered excessive and indicates that these women, as far as reproduction is concerned, belong to a high risk group. Hydramnios occurred 19 times; all (100%) the infants suffered from major congenital abnormalities and only two survive as a result of surgical treatment for oesophageal atresia. There is, at present, no evidence to show that the condition is hereditary.

The incidence of absent umbilical artery is 1% of all births and 7% of twin pregnancies.

The foetal loss in a consecutive series was 20% but in the total of 113 instances the foetal loss was 65 (58%). Fourteen of the 48 infants who survive are known to suffer from congenital abnormalities.

Major congenital abnormalities were present in 58 (51%) of the infants; only 40 (35%) were developmentally normal and a further 15 (14%) were thought to suffer from a congenital anomaly. The abnormalities were mostly multiple and not confined to any particular system. Obstructive lesions or atresia of the gastro-intestinal and urinary tracts were relatively common.

Fifty-six (59%) of the 95 viable infants of known weight were premature by weight at birth, but the average weight of all the infants at birth was less than normal. The placenta was considered to be abnormal in 32 (29%) of the pregnancies.

It is suggested that routine examination of the cut end of the umbilical cord at delivery might result in early diagnosis of some of the associated congenital abnormalities.

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Addendum

Since writing this article it has been discovered that one of the infants considered to be developmentally normal is, in fact, suffering from a marked degree of mental retardation.

THE NUMBER OF ALVEOLI IN THE TERMINAL RESPIRATORY UNIT OF MAN DURING LATE INTRAUTERINE LIFE AND CHILDHOOD

BY

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Until recently the child's lung was considered to be a miniature of the adult lung (Kölliker, 1881). Broman (1923) demonstrated that the bronchial tree underwent further branching after birth (in cows), that foetal alveolar ducts became bronchioles and that there was a postnatal increase of over 30% in the number of subpleural vesicles in the middle lobe of the right lung in rabbits and man.

Much work has been done on the minute structure of the terminal pulmonary units, of which Miller's book (Miller, 1947) is a landmark. Most of the research has been carried out on animals and no one, as far as we are aware, has worked on more than 15 children's lungs. No attempt appears to have been made to estimate postnatal alveolar growth on a quantitative basis. The present report records a statistical survey of the growth of the human terminal respiratory unit during the latter half of intrauterine life and through childhood.

Material and Methods

The lungs for study came from 2,500 necropsies carried out by the Department of Pathology at the Children's Hospital, Sheffield, during the years 1950-59. The routine necropsy practice at this hospital is to fix the lung while still attached to the heart and trachea. A block of tissue is then taken from each lobe at right angles to the direction of the main bronchus and at a distance of approximately one-third from the root of the lung to the periphery. If pathological lesions are suspected elsewhere in the lung, further blocks are taken.

The whole of the material was surveyed and the sections divided into categories indicating whether or not the lung showed gross pathology, and whether the tissues were well preserved and suitable for detailed study. The clinical histories were surveyed and all cases in which there was a congenital deformity of the heart, or a gross deformity of any other organ, were eliminated. This left approximately 600 well preserved lungs from apparently normally formed children. (Lungs showing a

small amount of oedema or areas of partial collapse were not eliminated provided the tissues were well preserved.)

Owing to the high mortality around birth all the lungs from older children were used and a random selection, based on necropsy number, from those dying during 36-40 weeks gestation. When the lungs were presented for histological assessment, the person examining the sections was not given details of the child's age or the cause of death.

Method of Assessment of Terminal Segment. Our concept of the terminal respiratory unit of the lung is of that mass of air spaces distal to a terminal respiratory bronchiole, the latter being a complete tube lined by epithelium. This, in Miller's (1947) classification, consists of the alveolar duct, atria and alveoli. Several methods of assessment were tried but the only one showing adequate reproducibility consisted of ignoring all the bronchioles completely lined by epithelium and noting only those lined by epithelium in one part of the wall. From the centre of such a respiratory tube, a perpendicular line was dropped on to the nearest and definite connective tissue septum (Fig. 1). This vertical line was made by using a single hair diaphragm in the eye-piece of the microscope. The number of alveoli cut by this line was then counted. This method overcomes, as far as is possible, the effects of varying degrees of collapse or of the presence of fluid or exudate in some alveoli. Ten such counts were done from each case. It is surprising how few such measurements can be taken from any one section. After all counts had been completed the means were correlated with age on a scatter diagram. The lungs from 309 children were examined in this way.

Fig. 1, showing sections from the lungs of a child of approximately 28 weeks maturity, and from a child of 11 months, illustrates the method of counting the alveoli.

Results

The final average figures in the different age groups, together with the errors of the means based upon the standard deviations and number of cases, are given in the Table and shown graphically in

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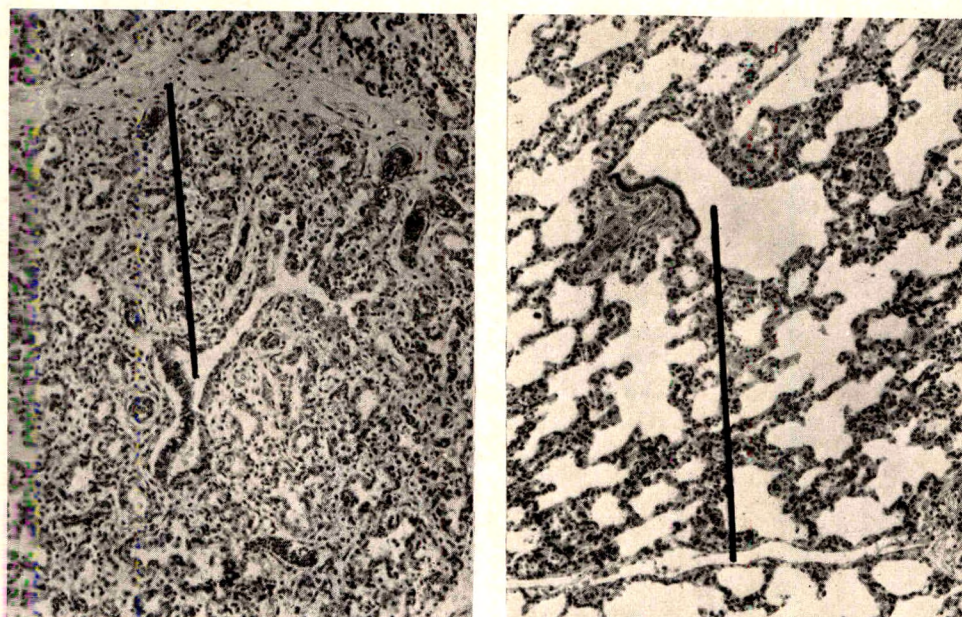


FIG. 1.—Photographs of lungs to illustrate the method of counting: one from a child of 28 weeks gestation (left) and the other from a child of 11 months (right). The black line indicates the position of the hair line as used under the microscope.

TABLE
ALVEOLAR COUNTS

Age Group	No. of Cases	Radial Alveoli Count (mean)	S.D.	S.E. of Mean	Estimated Number of Alveoli for Terminal Lung Unit
Gestational					
24-27 weeks	6	2.2	0.60	0.19	42
28-31 weeks	12	2.6	0.80	0.20	
32-35 weeks	10	3.2	0.90	0.20	130
36-39 weeks	9	3.6	0.90	0.20	
Birth (40 weeks)	25	4.4	0.90	0.17	340
1 wk-4½ mths	38	5.5	1.38	0.21	
5-9 mths	25	6.6	1.68	0.34	
10-15 mths	34	7.0	1.68	0.22	1,370
15-22 mths	28	7.1	1.75	0.22	
23-30 mths	28	7.2	1.42	0.19	
2 yrs 7 mths-3 yrs 6 mths	25	7.3	1.42	0.19	1,556
3 yrs 7 mths-4 yrs 6 mths	15	7.5	1.52	0.39	
4 yrs 7 mths-5 yrs 6 mths	13	7.6	1.12	0.31	1,715
5 yrs 7 mths-6 yrs 6 mths	8	7.8	1.31	0.28	
6 yrs 7 mths-7 yrs 6 mths	9	8.0	1.31	0.28	
7 yrs 7 mths-8 yrs 6 mths	4	8.2	1.50	0.28	2,200
8 yrs 7 mths-9 yrs 6 mths	5	8.5	1.70	0.35	
9 yrs 7 mths-10 yrs 6 mths	6	8.7	1.80	0.40	2,630
10 yrs 7 mths-11 yrs 6 mths	4	9.0	1.82	0.40	
11 yrs 7 mths-12 yrs 6 mths	5	9.3	2.00	0.40	3,220

Note: Gestational age, based upon the last menstrual period, is used up to birth and postnatal age after birth.

Fig. 2. There is very great variability between children of the same age; some lungs were found from children of 2 years of age showing a similar alveolar count to that of children of 10 years. There is an increase in the alveolar count throughout the whole of childhood. The radial alveolar count

goes from approximately 2.5 at 28 weeks of gestation to 4.4 at full term. By the age of 1 year, the alveolar count increases to nearly seven. This increase continues in an apparently uniform way throughout the whole of childhood, until it reaches between eight and nine at the period just preceding

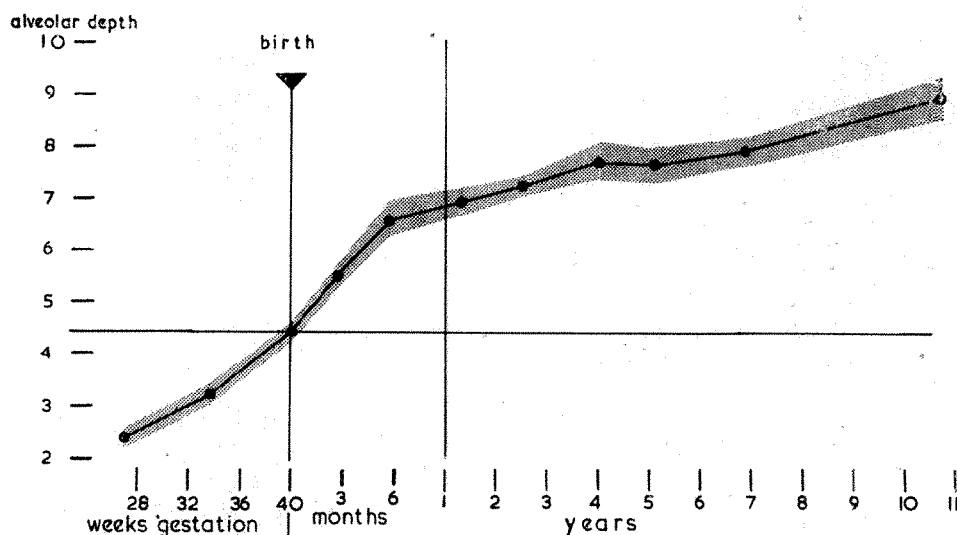


FIG. 2.—Graph showing the mean and standard error of mean of the radial alveolar counts ('alveolar depth'), related to age.

puberty. Unfortunately we were unable to continue our examination into the older age group, there being no suitable material available to us.

The counts given here represent the number of acini cut by an apparent random 'radius' within the terminal respiratory unit. The latter probably varies in form but basically is a compressed sphere. If this terminal unit were a sphere, the number of alveoli in it would be given by the formula $\frac{2}{3}n^3$, i.e. approximately $2.1n^3$ (where 'n' is the number of alveoli cut by the radius). If the terminal unit were a cube, 'n' would represent a half of the length of a side and the alveolar count $(2n)^3$, i.e. $8n^3$. The formula for a sphere represents the smallest theoretical number and that for the cube by no means the largest. If we take, for convenience, $4n^3$, this gives the terminal respiratory unit at full term $4 \times (4.4)^3 = 340$ alveoli. At 1 year this becomes 1,370, and at 10 years 2,900, i.e. an apparent nine-fold increase.

Discussion

There is now no doubt that the ideas that the lungs are fully formed by 6 months' gestation, and that the act of breathing is responsible for later difference in appearance (Barnard and Day, 1937) or that the lung is mature at birth (Norris, Kockenderfer and Tyson, 1941), are false. We have found that the terminal respiratory unit contains apparently nine times as many alveoli at the age of 10

years as at birth. This does not represent the full rate of development as this assumes that the total number of terminal units remain the same. Willson (1928) showed that in white mice there was an increase in the number of branches of the respiratory tree from 21 and 23 in the newborn to 29 and 30 in the adult and, from the study of sections from lungs of 15 children, stated that the human lung tree showed a similar increase branching after birth. Bremer (1935) working on opossum lungs suggested that the bronchioles grew distally by muscularization and epithelialization of the alveolar ducts so that what were at one time alveolar ducts, later became respiratory bronchioles. This view was also held by Broman (1923). Animals apparently vary considerably in the degrees of relative lung maturity at birth (Broman, 1923; Engel, 1953), and thus animal studies are not directly applicable to man in this respect. It has been shown quite conclusively (Cohn, 1940) that in the rat, there is an active production of new alveoli in compensative hypertrophy of a lobe in response to the removal of another lobe of the same lung. Evidence regarding alveolar growth in man is very scanty and rests largely on finding mitotic figures in the lining cells of alveoli and respiratory tubules in infants. Palmer (1936) found 17 generations of respiratory tubes in the human newborn and Broman (1923) suggested that there were six to seven further generations found after birth. This gives 131,000 (2^{17}) terminal respiratory units at birth and 2^{24} ,

i.e. 1,677,000 in the mature lungs (a 127-fold increase in terminal units!). We have demonstrated that there is a nine-fold postnatal increase in the number of alveoli in the terminal unit. Thus there is a theoretical overall increase of $9 \times 127 = 11,243$, i.e. an increase of more than 10,000-fold after birth, which is much greater than that of the circulating blood cells. It is of interest that Willson (1928) considered that the air spaces in the young child were larger than in the adult, and suggested that children were normally in a state of relative emphysema. Dubreuil, Lacoste and Raymond (1936) considered that the lung of the newborn consisted of alveolar ducts only and that all of the alveoli developed after birth.

The method of alveolar multiplication is not certain. It has been suggested that the new alveoli are formed *in utero* by the production of septa across the existing saccula (Loosli and Potter, 1951). Ham and Baldwin (1941), who worked chiefly on pigs' lungs, looked upon the lung in Macklin's concept (1936), as being a structure in a state of functional interstitial emphysema, and they considered that new alveoli were not produced by the peripheral cells, but by the splitting of the alveolar walls and the penetration of air between the beds of capillaries in a kind of progressive, controlled interstitial emphysema. The now well established presence of a lining membrane to all alveoli, does not really invalidate their concept as a thin membrane could well be ballooned into the interstitial space. Fried (1956) from a study of rabbit lungs, considered that the interstitial cells of the alveolar septa, as well as becoming the intra-alveolar phagocytes, were also capable of forming alveolar walls themselves. Krah1 (1955), following up the electron-micrographic studies of the lining membranes of the alveoli made by Low (1953), took the problem of development no further than Miller (1947) or Morison (1952) in showing that the epithelium of the peripheral alveoli was less attenuated than the most central ones.

The importance of the postnatal development of alveoli will be appreciated when we consider the possibility of factors such as air pollution or repeated respiratory infections interfering with alveolar

proliferation and resulting in adults with a diminished reserve of alveoli.

Summary

A systematic and statistical study has been carried out on the lungs of children dying during the later part of gestation and through childhood up to 12 years of age.

An estimate has been made of the number of alveoli in the terminal respiratory unit and this shows a rapid increase during the first year after birth and a steady increase throughout childhood, there being apparently a nine-fold increase in the alveoli after birth.

If consideration is also given to the increased proliferation of the respiratory tree after birth, there is the possibility of a thousand-fold increase in the number of alveoli between birth and puberty.

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CORRELATION BETWEEN BIRTH WEIGHT AND CLINICAL FINDINGS IN DIPLEGIA

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Since the time of Little the role of birth injury in the aetiology of cerebral palsy has been much debated (Little, 1843; 1862). Freud and Collier believed that diplegia often had its origin in prenatal life and was less frequently the result of birth injury than was generally thought (Freud, 1897; Collier, 1899, 1924). More recently attempts have been made to classify diplegic patients into two main groups:

(1) Those who are delivered prematurely and who tend to suffer from paraplegia. This group shows, on the whole, normal intelligence and no other neurological abnormalities.

(2) Those of approximately average birth weight who show upper as well as lower limb involvement. This group tends to show mental impairment and other neurological defects (Childs and Evans, 1954; Churchill, 1958; Polani, 1958).

The birth weight distributions of patients suffering from congenital paraplegia or tri- and tetraplegia are generally found to be biphasic. It has been suggested that this provides further evidence in favour of there being two major aetiological groups of diplegic patients (Childs and Evans, 1954).

In the present study, the birth weight distribution of 200 diplegic patients was analysed and correlated with the clinical findings.

Terminology

Diplegia is used to describe a more or less symmetrical paresis of cerebral origin, more severe in the lower limbs than in the upper. The paresis may be accompanied by hypotonia, rigidity or spasticity of the affected limbs. Patients with marked involuntary movements or ataxia were not included. The patients were placed in two categories:

(1) Paraplegics, in whom the upper limbs were functionally normal, even though minor neurological abnormalities were apparent in them.

(2) Tri- and tetraplegics in whom there was some functional involvement of one or both upper limbs (Balf and Ingram, 1955).

Selection of Patients and Methods of Study

The series comprised 200 diplegic children referred to the Edinburgh Clinic of the Scottish Council for Care of Spastics; 58.5% were males and 41.5% females. Their ages ranged from 14 months to 13 years.

Patients may be referred to this clinic by school medical officers or general practitioners from any part of Scotland. Since many patients were sent because they were believed to be suitable candidates for a special school designed to cater for severely physically affected children of average intelligence, the series was highly preselected. At the clinic detailed histories were taken and examinations made by a neurologist, psychologist and orthopaedic surgeon. In addition to having access to the records of the clinic the parents were interviewed and patients examined personally in all but a few instances. Any patients in whom a postnatal cause for the condition was probable were excluded.

Findings

Birth Weights. Birth weights were obtained in the majority of cases from hospital or nursing home records and in the remainder from questioning parents. The mean birth weight of 88 paraplegic patients was 5.1 lb. (S.D. 0.23), and of 112 tri- and tetraplegic patients was 6.1 lb. (S.D. 0.2). The frequency distribution of birth weights in both groups shows a bimodal curve (Fig. 1). The distribution of birth weights in the general population showing a unimodal curve is given for comparison. This distribution was obtained from a series of live births in an Edinburgh hospital (Drillien and Richmond, 1956), allowance then being made for infant mortality. The paraplegics show a major peak at about 4 lb. and a smaller one at 8 lb. In the tri-

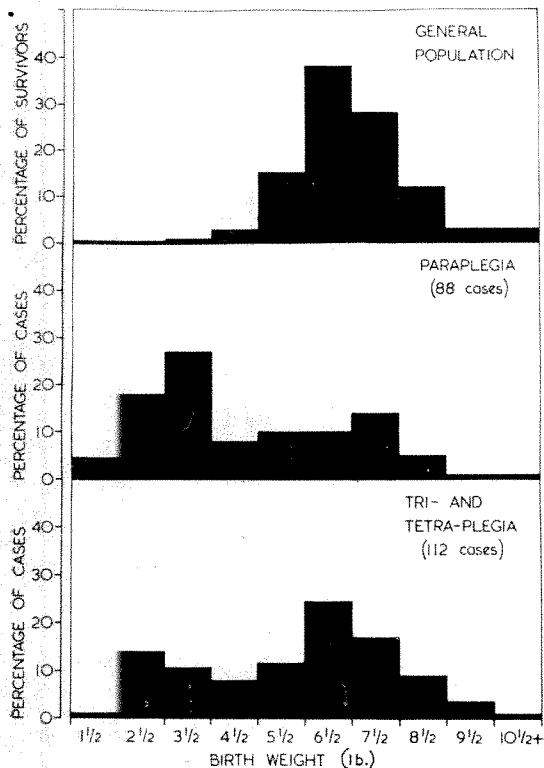


FIG. 1.—Distribution of birth weights in two groups of diplegic patients compared to the distribution in the general population.

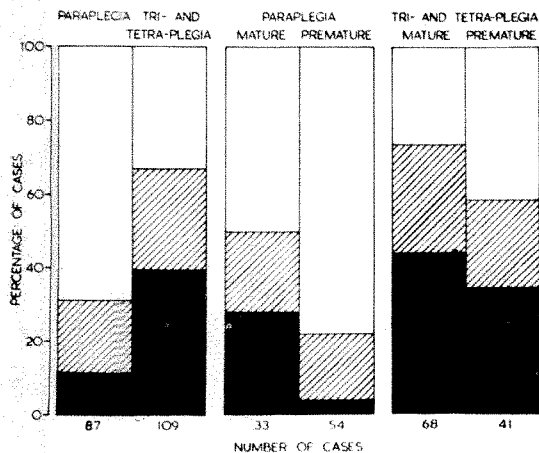


FIG. 2.—Comparative intelligence of mature and premature paraplegic, tri- and tetraplegic patients.

□ normal ▨ retarded ■ ineducable

and tetraplegic group on the other hand, the main peak is in the region of 7 lb. with a lesser rise at 3 lb. Thus paraplegic patients, as a group, tend to be premature, whereas patients with upper limb involvement tend towards average birth weights.

Intelligence. The intelligence of the two groups was compared on the basis of the psychologist's assessment and patients were divided into three groups:

(1) 'Normal': Those educable at a normal school or a special school catering for children of average intelligence but with physical handicaps. Arbitrarily, children with an I.Q. of 80 or above were placed in this category.

(2) 'Retarded': Those unlikely to benefit from education at schools for children of average intelligence and who were usually best placed in schools for the mentally or physically handicapped. The majority in this group have an I.Q. above 60 but below 80.

(3) 'Ineducable': Patients whom it is impossible to educate, some of whom may be suitable for training in occupation centres. An I.Q. of less than 60 forms the criterion for classifying patients in this category.

Four children, who were considered too young for an estimate of educability to be made were excluded from the analysis. From Fig. 2 and the Table it will be seen that paraplegic patients, as a group, are more intelligent than those with upper limb involvement. The difference between these two groups is highly significant statistically ($p = <0.001$). If the patients are further subdivided into mature and premature (the criterion of prematurity being a birth weight of $5\frac{1}{2}$ lb. or less), it is evident that, within each group, patients of smaller birth weight tend to be more intelligent than those of larger birth weight. However, although the difference between the mature and premature paraplegics is significant ($p = 0.01$), there is not a statistically significant difference between the two groups of tri- and tetraplegic patients.

Epilepsy. The incidence of epilepsy among paraplegic patients was 9% (eight cases in 88), whereas in the tri- and tetraplegic group it was 26.8% (30 cases in 112).

Strabismus. No significant difference was found in the incidence of strabismus in the two groups.

As a corollary to the above findings one would expect the birth weight distribution of patients with mental defect and/or other neurological abnormalities (who are thought to represent a distinct

TABLE
INTELLIGENCE OF PARAPLEGICS AND TRI- AND TETRAPLEGICS

Group	No. of Cases	Normal (%)	Retarded (%)	Ineducable (%)
Paraplegia	87	68.9	19.6	11.5
Matures (>5½ lb.)	33	50	22	28
Prematures (5½ lb. and under)	54	78	18	4
Tri- and Tetraplegia	109	33	27.5	39.5
Matures (>5½ lb.)	68	26.5	29.4	44.1
Prematures (5½ lb. and under)	41	41.5	24.4	34.2

group) to show a unimodal curve. Similarly, the birth weight distribution of patients of normal intelligence who are without other neurological defects should also be unimodal (Churchill, 1958; Polani, 1959). When birth weights in these groups were analysed, the bimodality became less marked, but did not entirely disappear (Fig. 3).

The mean birth weights of the two groups differed, being 6.1 lb. (S.D. 3.1) in patients showing mental impairment and/or epilepsy and 5.0 lb. (S.D. 3.7) in the group which did not show these abnormalities.

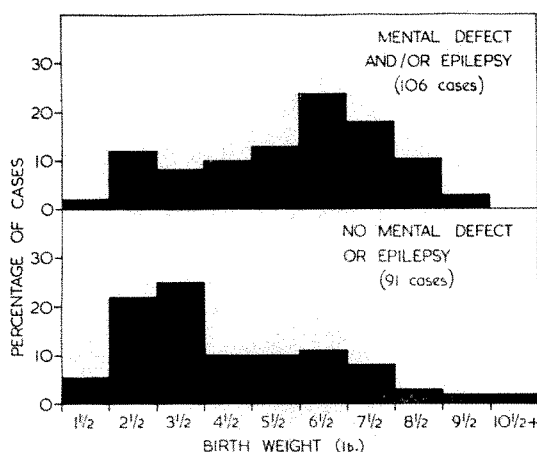


FIG. 3.—Distribution of birth weights related to presence or absence of mental defect and epilepsy.

Discussion

When birth weights of a group of paraplegic patients and a group of tri- and tetraplegic patients were analysed the distributions in each group were bimodal. Paraplegic patients tended to be smaller at birth, more intelligent and less liable to complicating neurological abnormalities than those with upper limb involvement. Tri- and tetraplegic patients were larger at birth but more often suffered from mental retardation and epilepsy. The greater extent of their limb involvement and other clinical

manifestations suggested that brain damage was more extensive than in those with paraplegia. It has been suggested that these differences in clinical findings may be correlated with differences in aetiology in the two groups. Both the premature birth and the relatively localized cerebral damage in the paraplegic patients may be the result of damaging factors operating *in utero*. Possibly the prematurity, *per se*, contributes to the cerebral palsy by depriving the nervous system of the intra-uterine environment essential for its normal maturation (Polani, 1958). The more extensive cerebral involvement of the tri- and tetraplegic group may be attributed, in some cases, to birth trauma. However, even when there is a history of difficult delivery, birth trauma cannot necessarily be incriminated as foetal abnormality may have been the cause of the abnormal parturition.

Summary

The birth weights of 88 paraplegic patients and 112 tri- and tetraplegic patients were analysed and correlated with clinical findings. Patients with paraplegia, on the whole, were found to be considerably smaller at birth, more intelligent and showed a lower incidence of epilepsy than the group of patients with upper limb involvement. The distribution of birth weights in both groups was bimodal. When the birth weights of the entire group were analysed according to the presence or absence of mental defect and epilepsy, it was found that most of the patients with mental impairment or epilepsy were of average or high birth weights and tended to show upper as well as lower limb involvement. Those who showed no other neurological abnormalities tended to be paraplegic patients of premature birth. Patients with diplegia can be segregated into two fairly well defined groups which probably differ aetiologically as well as clinically.

I am indebted to the Scottish Council for Care of Spastics for granting facilities and financial support for this investigation and to their medical consultants in Edinburgh, Mr. G. A. Pollock, Dr. J. A. Naughton and Dr. T. T. S. Ingram, for allowing me to use their case

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SUGARS IN THE BLOOD AND URINE OF CHILDREN FOLLOWING THE INGESTION OF DISACCHARIDES

BY

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It has previously been shown that reducing sugars are frequently excreted in the urine by mature and premature newborn babies (Haworth and McCredie, 1956; Haworth and MacDonald, 1957). Other workers, using paper chromatographic methods, have also found small amounts of sugars in the urines of children and usually higher concentrations of lactose and galactose in urines from young babies (Woolf, 1951; Apthorp, 1957; Bickel, 1959). Coant, Glowacki and Reardon (1959) found a high urinary excretion rate of sugars by premature babies which could be correlated with the amount of lactose in the feedings.

This paper describes further observations on sugars in the urine and blood of newborn babies and older children following the oral ingestion of different disaccharides.

Analytical Methods

The chromatographic technique employed for the separation of sugars in blood and urine was the same as that used previously (Haworth and McCredie, 1956; Haworth and MacDonald, 1957), being a modification of the method originally described by Williams (1954). The filter papers were bisected after removal from the solvent and one half was sprayed with a benzidine developer and the other half with a phloroglucinol reagent (Horrocks and Manning, 1949). Glucose, fructose, lactose, galactose and pentoses were identified by the former reagent and sucrose by the latter. With a double application of the test substance, monosaccharides could be identified in concentrations of about 10 mg./100 ml. and disaccharides in rather lower concentrations.

Blood sugar estimations were performed by the method of King (1951).*

Part I: Sugars in Urine and Blood of Mature and Premature Babies Following Ingestion of Disaccharides

Clinical Material and Methods. The sugars lactose, sucrose or maltose were fed to 47 newborn babies at

the Women's Pavilion of the General Hospital, Winnipeg. The group was unselected, except that males were preferred to females because of the greater ease of urine collection. There were 39 males and eight females. Twenty-eight of the babies were mature and 19 were premature (birth weight $5\frac{1}{2}$ lb. or less). All the babies were considered healthy with the exception of two (one mature and one premature) who developed hyperbilirubinaemia which was not due to any demonstrable blood incompatibility between mother and child. Neither, however, required exchange transfusion. Five other babies developed mild 'physiological' jaundice. The birth weights of the babies varied between 3 lb. 1 oz. and 11 lb. 6 oz. and the estimated gestation of the premature babies was from 30 to 40 weeks. The ages of the babies at the time of the tests were between 1 and 23 days.

The sugars were fed in doses ranging from 0.5 to 4.2 g. per lb. at the baby's usual feeding time, i.e. three or four hours after the previous feed. In 10 instances the test sugar was given in the baby's usual feed (expressed breast milk or evaporated milk) and the additional sugar in the feed was taken into account in calculating the total dose given. In all the other experiments the sugar was given in water. The sugars were administered to several of the smaller premature babies by gavage. The dose of the sugar given was assessed approximately, allowances being made for the baby who was unable to take the total volume of fluid and for minor regurgitations. Tests were abandoned in babies who vomited.

Test tubes for urine collection were applied to the babies one hour before the test feed and specimens collected in this interval were termed 'a.c.' urines. Test tubes were reapplied at the end of the feeds and left in place until the babies voided. These specimens were the 'p.c.' urines. Some babies did not pass urine for as long as six hours after the test feed and, because it was not justifiable to withhold feedings longer than this, some 'p.c.' urines were not obtained. It was also not possible to collect the 'a.c.' urine in every instance.

Capillary blood was collected for chromatography before the test feed and one and two hours after the conclusion of the feed. In a few tests half-hour and three-hour specimens were also taken.

Results. Sixty-two tests were conducted on the 47 babies and the results are summarized in Tables 1 to 4.

* It has been found that this method measures 100% glucose, 85% fructose, 68% galactose and 28% lactose.

TABLE 1
SUGAR CONTENT OF A.C. URINES FROM MATURE AND
PREMATURE BABIES

	Urine Containing Sugar	Urine Containing No Sugar	Total
Mature	5	20	25
Premature	8	16	24
Totals	13	36	49

URINES. Table 1 shows the sugar content of the 49 'a.c.' urines that were collected during the 62 tests. Thirteen of these urines contained one or more sugars and 36 contained no sugar. Two urines contained lactose alone, four galactose alone, five galactose and lactose, one glucose alone and one glucose and lactose. There was no statistically significant correlation between the proportions of urines which contained sugars and the maturity of the babies.

Table 2 shows the number of observations obtained by feeding lactose, sucrose and maltose and the subsequent urine sugar content. There was no statistical difference in the sugar excretion rate of the mature and premature babies. It is seen that following a feed of lactose, this sugar was found in eight of the 12 urines excreted by the mature babies and in six of 15 urines excreted by the premature babies. After sucrose feeding,

three of six urines from mature babies and two of eight urines from the prematures contained sucrose. Monosaccharides were similarly found as frequently in the urines of the mature as of the premature infants. After receiving a feed of maltose, none of the 14 'p.c.' urines showed this sugar, although, nine urines contained glucose.

There was no correlation between the dose of the sugar administered and the subsequent urinary sugar content as shown in Table 3. The premature babies received on the whole higher doses than the mature babies. For instance, of 17 premature babies who received lactose on one or more occasions, eight received less than 2 g. per lb. and nine 2 or more g. per lb., while 13 mature babies received the lower dose and only one the higher.

Pentoses were found in two urines. These were not identified with certainty but may have been xylulose. Xylose was not found on any occasion in this series. The concentration in which the sugars were found in the 'p.c.' urines are expressed in Table 4. It may be seen that sugars were most commonly present in concentrations below 200 mg./100 ml., but glucose, fructose and sucrose were occasionally found in higher concentrations. A 'trace' indicates that there was a very clear but faint band on the filter paper, showing monosaccharides in a concentration of about 10 mg./100 ml. and disaccharides in a somewhat lower concentration. There was no

TABLE 2
SUGARS FOUND IN THE BLOOD AND URINE AFTER FEEDING LACTOSE, SUCROSE OR MALTOS
TO 47 NEWBORN BABIES

	Lactose			Sucrose			Maltose		
	Mature Babies	Premature Babies	Total	Mature Babies	Premature Babies	Total	Mature Babies	Premature Babies	Total
No. of Patients. . . .	14	13	27	7	6	13	9	6	15
Urines:									
No. of tests	14	17	31	7	9	16	9	6	15
No. examined	12	15	27	6	8	14	9	5	14
Glucose	5	0	5	0	5	5	5	4	9
Galactose	6	11	17	0	0	0	0	0	0
Lactose	8	6	14	0	0	0	1	1	2
Fructose	0	1	1	5	4	9	0	0	0
Sucrose	0	0	0	3	2	5	0	0	0
Pentose	0	0	0	0	1	1	0	0	1
No sugar	3	2	5	1	2	3	4	1	5
Blood:									
No. of tests*	4	14	18	1	5	6	0	2	2
Glucose	4	14	18	1	5	6	0	2	2
Other sugars	0	0	0	0	0	0	0	0	0

* Fasting and usually one- and two-hour specimens.

TABLE 3
SUGAR CONTENT OF 'P.C.' URINES RELATED TO THE DOSE OF SUGAR ADMINISTERED

Dose	Sugar Given	No. of Urines	No. of Urines Con- taining No Sugar	Disaccharide*	Monosaccharide*
<2.0 g./lb.	Lactose	18	3	11	11
	Sucrose	8	3	3	5
2.0 g./lb. or more	Lactose	9	2	3	11
	Sucrose	6	0	2	9

* Indicates the number of sugars found in the urines, i.e. several urines contained more than one sugar.

correlation between the concentration of sugar in the urine and the dose administered or the maturity of the baby. Two of the babies excreting the largest amount of sucrose were mature and had received less than 2 g. per lb. sucrose, the other was a premature who had taken more than 2 g. per lb.

The jaundiced babies behaved no differently from the other babies with respect to sugar excretion.

TABLE 4
CONCENTRATIONS OF SUGARS IN P.C. URINES

Concentration (mg./100 ml.)	No. of Urines Containing Sugars				
	Glucose	Galac- tose	Lactose	Fruc- tose	Sucrose
Trace	5	7	3	—	1
<100	4	5	5	—	—
100-200 ..	8	5	8	9	1
>200	2	—	—	1	3
Totals	19	17	16	10	5

BLOODS. Bloods were chromatographed during 26 tests on 19 babies and, as shown in Table 2, no sugar other than glucose was found.

Part II: Sugars in Urine and Blood of Older Children Following Ingestion of Disaccharides

Clinical Material and Methods. The subjects were 47 in-patients in the Children's Hospital, Winnipeg, ranging in age from 5 months to 15 years. There were 24 males and 23 females. The children were carefully selected and were as 'normal' as possible. Many of the children were suffering from minor skin infections, some were in hospital for investigation of such conditions as convulsions and others were convalescent from infections such as pneumonia. None of the children had had elevated temperatures for 48 hours before the tests, none were taking drugs, such as hormones, which might have had an effect upon their metabolism and none were suffering from any metabolic disorder. Patients with gastro-intestinal disease were not included with the exception of four children who were carriers of *E. coli* or salmonella organisms. These four children had had normal bowel movements for at least one week preceding the tests and were all said to have normal appetites. They were receiving standard hospital diets but otherwise the carbohydrate intake before the tests was not controlled.

The tests were performed at 9 a.m. after the subjects had been fasted from midnight. After the fasting blood specimens had been taken the children drank the sugars dissolved in water flavoured with lemon. The dose of the sugar administered was 1 g. per lb. body weight, the minimum dose 15 g. and the maximum 50 g. Further blood specimens were initially taken half, one and two hours after the feed and in later experiments an additional quarter-hour specimen was also taken. These bloods were chromatographed and analysed for total sugar content. From eight of the children, five and 10-minute bloods were also analysed for total sugar.

Urines for chromatography were collected one hour after the test feed, but in some of the children no sample was obtainable.

Five additional 'normal' children (four males and one female) whose ages ranged from 6 weeks to 21 months were given lactose by mouth under the same conditions as detailed above. Immediately following the feed, urine collection was started and continued for eight hours. An approximate quantitative estimation by paper chromatography was made of the sugars in each of the urines.

Results. Eighteen children received lactose, 22 sucrose, and seven maltose.

The results of paper chromatographic analysis of the urines and blood are shown in Table 5. It can be seen that 12 of the 15 urines obtained from the 18 children who were given lactose contained sugars (lactose was present in six of them) and only three contained no sugar. In an 18-month-old girl a trace of lactose was found in the 15-, 30- and 60-minute blood samples, but not in the fasting and two-hour samples. No lactose was found in the urine of this child. In 16 urines, collected from 22 children who were given sucrose, fructose was identified in eight, five of which also contained sucrose. The remaining eight urines contained no sugar.

Sucrose and fructose were found together in the blood of four children. These were different children from the five who excreted this combination of sugars in the urine, although two of these five children showed fructose alone in the blood. Glucose was naturally also present in all the blood samples chromatographed. Maltose was not found in the blood or urine of any of the seven children who had received this sugar. A trace of glucose was present in one of the seven urines, the others contained no sugar.

The concentrations of the sugars found in the urine were all between 50 and 100 mg./100 ml. except for a 5-month-old baby who excreted approximately 120 mg. of lactose per 100 ml. The sucrose and/or fructose

TABLE 5
SUGARS IN BLOOD AND URINE AFTER FEEDING LACTOSE, SUCROSE OR MALTOSE TO 47 CHILDREN

	Sugar Administered		
	Lactose	Sucrose	Maltose
No. of patients	18	22	7
'p.c.' Urines:*	15	16	7
Glucose	1	1	1
Galactose	11	0	0
Lactose	6	0	0
Fructose	0	8	0
Sucrose	0	5	0
No sugar	3	8	6
Blood:			
Glucose	18	22	7
Galactose	0	0	0
Lactose	1	0	0
Fructose	0	6	0
Sucrose	0	4	0

* Figures indicate number of sugars found in the urines, i.e. several urines contained more than one sugar.

TABLE 6
AGES OF 40 CHILDREN GIVEN LACTOSE AND SUCROSE IN RELATION TO SUGARS
FOUND IN BLOOD AND URINE

Sugar Fed	Age	No. of Cases	Sugar Excreted	No Sugar Excreted	No Urine Collected	Sugar* in Blood	No Sugar* in Blood
Lactose	5-11 mths	5	2	1	2	0	5
	1-3 yrs	6	4	1	1	1	5
	4-8 yrs	3	2	1	—	0	1
	>8 yrs	4	4	0	—	0	4
Sucrose	5-11 mths	4	3	0	1	1	3
	1-3 yrs	10	3	4	3	4	6
	4-8 yrs	4	2	1	1	1	3
	>8 yrs	4	0	3	1	0	4

* Other than glucose.

identified in the blood of six children were only present in 'trace' amounts which corresponded to concentrations of about 20 mg./100 ml.

Table 6 shows the ages of the 40 children who were given lactose and sucrose in relation to the sugars found in the urine and blood. The older children who were given lactose excreted sugars to the same degree as the younger and no relation between age and sugar excretion was demonstrated. No sugar, however, was found in the three urines obtained from the four children over the age of 8 years who were given sucrose, and no fructose or sucrose was found in their blood. The five children who excreted sucrose were all under 3 years of age. Sucrose and fructose were found in the blood of an 8-year-old boy, but unfortunately no urine specimen was obtained from this child.

Table 7 and Fig. 1 show the mean blood sugar levels following feeding the three sugars. On 18 occasions blood sugar levels were obtained 15 minutes after the test feed as shown in column 6 of Table 7 and by the separate points in Fig. 1. The 15-minute levels following the administration of lactose were higher than the 30-minute levels, but for the other two sugars the 'peak' was at 30 minutes. The differences between the 30-minute levels following the administration of sucrose (143 mg./100 ml.) and lactose (116 mg./100 ml.) are statistically significant ($p = <0.01$). The differences between the 30-minute levels of the sucrose and maltose curves, the maltose and lactose curves, and the levels at other time intervals are not statistically significant. Five- and 10-minute blood sugar levels were also obtained in four subjects following the administration of lactose and in four following sucrose. The mean

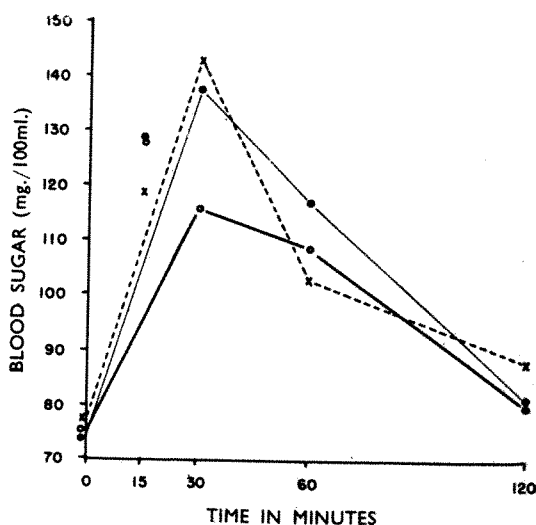


FIG. 1.—Mean blood sugar levels following the oral ingestion of lactose, sucrose and maltose (fastings 15-, 30-, 60- and 120-minute levels).

○ — mean levels after lactose, all cases (18)
 × — mean levels after sucrose, all cases (22)
 ● — mean levels after maltose, all cases (7)

levels are shown in columns 4 and 5 of Table 7 and the mean blood sugar levels of these eight children are expressed in Fig. 2.

Table 8 shows the approximate amounts of galactose and lactose excreted over an eight-hour period by the five young children who were given lactose by mouth. It can be seen that the total amounts excreted were very small, 120 mg. of lactose in the urine of Case 3 being the largest amount found.

Discussion

The results obtained in Part I confirm the earlier findings that sugars are frequently excreted in the urine of newborn babies (Haworth and McCredie,

TABLE 7

MEAN BLOOD SUGAR LEVELS (mg./100 ml.) OF 47 CHILDREN
GIVEN LACTOSE, SUCROSE AND MALTOSE BY MOUTH

Sugar Fed	No. of Tests	Fasting	Time after Ingestion (min.)					
			5	10	15	30	60	120
Lactose	18	75	101 (4)	108 (4)	128 (9)	116	109	80
Sucrose	22	77	103 (4)	113 (4)	119 (6)	143	103	88
Maltose	7	74	—	—	129 (3)	138	117	80

Numbers in parenthesis indicate the number of children upon whom 5-, 10- and 15-minute estimations were obtained.

TABLE 8
TOTAL AMOUNTS OF SUGAR EXCRETED OVER EIGHT HOURS BY FIVE CHILDREN
FOLLOWING DOSE OF LACTOSE BY MOUTH

Case No.	Age (mths)	Sex	Weight lb. oz.	Dose of Lactose (g.)	Volume of Urine (ml.)	Total Sugar Excreted (mg.)	
						Lactose	Galactose
1	1½	F	11 4	15	41	8	8
2	6	M	17 0	17	49.5	7.5	7.5
3	21	M	34 0	35	97	120	43
4	¼	M	6 6	15	89	18	11
5	2	M	11 2	20	127	19	19

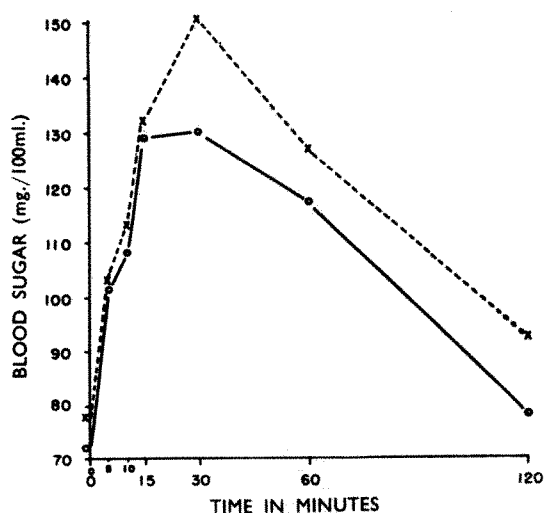


FIG. 2.—Mean blood sugar levels following the oral ingestion of lactose and sucrose (fastings 5-, 10-, 15-, 30-, 60- and 120-minute levels).

○ — ○ mean levels after lactose (4 cases)
× - - - × mean levels after sucrose (4 cases)

1956; Haworth and MacDonald, 1957). Part II shows that older children also frequently excrete sugars after the ingestion of sugars by mouth.

With the exception of the pentoses which were found in two newborn urines, there can be little doubt that the urinary sugars originated from the gut because there was such a close association between the sugar ingested and that subsequently found in the urine. In Part I more urines contained sugars after the sugar feed (Table 2) than those collected before the feed (Table 1). It seems likely that the galactose, glucose and lactose found in 13 of these 49 'a.c.' urines were derived from the milk feeds these babies had received three to four hours before the tests were performed. Tables 2 and 5 show that the sugar fed to the babies in Part I and the older children in Part II had a considerable

influence on the type of sugar excreted in the urine. Sucrose was never found unless sucrose had been fed and galactose was never found unless lactose had been fed. In Part I lactose was found in the urine of two babies who had received maltose, but it is again likely that this was the result of preceding milk feeds. Fructose was found on one occasion after a lactose feed, but this baby's previous feed had contained sucrose.

That some lactose may escape hydrolysis in the gut and subsequently appear in the urine has been known for many years (Folin and Berglund, 1922; Winter, 1931; Koehler, Rapp and Hill, 1935). The investigations reported here show that it is a very frequent occurrence in babies and children. Although as much as 200 mg. of lactose per 100 ml. was found in the urine of some babies, Table 8 indicates that the amount of lactose excreted in the urine during an eight-hour period was only a very small fraction of the total dose given to these five babies.

Galactose, which together with glucose, is released by the hydrolysis of lactose is thought to be transported to the liver where it enters the 'glucose pool'. If the load of galactose entering the liver by the portal vein is too great for that organ to metabolize, some of the sugar will escape into the systemic circulation and because there is no renal threshold for galactose (Hartmann, McCoy, Swarm and Nakasato, 1954), it will be excreted. Rowe (1924) found that 30 g. was the maximum dose of galactose that could be ingested by adults without galactose appearing in the urine. Folin and Berglund (1922) found that the ingestion of only 10 g. could cause sugar to be excreted. Shay, Schloss and Bell (1931), on the other hand, found no correlation between the age, weight or dose given to their subjects and the subsequent amount of galactose excreted in the urine. No relation between the dose of sugar given and the urinary excretion of sugar could be demonstrated in the tests on the babies in Part I (Table 3).

Sucrosuria following the oral ingestion of sucrose has been recognized by other workers (Murschhauser,

1921; Elmer, Krasowska and Ptaszek, 1939; Lahdensuu, 1947). A dose of sucrose 2 g. per kg. body weight was considered by some to be the upper limit of tolerance. Again, no relation between the dose given and sugar excretion was demonstrated in the observations reported here. Several babies who were given more than 2 g. sucrose per lb. body weight (Table 3) and several older children who received 1 g. per lb. did not show sucrosuria. Any sucrose escaping hydrolysis in the gut is evidently treated after absorption as a foreign substance and excreted (Keith, Wakefield and Power, 1932; Keith and Power, 1937). Sucrose was identified in five of 14 urines collected from newborn babies and in five of 16 urines from older children who had received this sugar (Tables 2 and 5). Three of the babies excreted the sugar in a concentration greater than 200 mg. per 100 ml. (Table 4). Sucrosuria of such a degree, occurring in approximately a third of these children after sucrose feeding, raises doubts as to the significance of the findings of sucrosuria in the cases reported by Reiner and Weiner (1939), Owen and Lewis (1956), and the syndrome of hiatus hernia, mental defect and sucrosuria described by Moncrieff and Wilkinson (1954) and Woodruff (1958). Certainly the degree of sucrosuria exhibited by the children which these authors recorded was no more than that shown by the normal children reported here. Perry, Lippman, Walker and Shaw (1959), who recently reported findings very similar to mine, came to the same conclusion. Moncrieff and Wilkinson (1954) stated that when sucrose and lactose were given together in the diet of their patients, other sugars were excreted more easily in the urine. I have no additional observations to make about this statement except to emphasize that normal children apparently excrete sugars so frequently after sugar-containing feedings.

It is noteworthy that maltose was never found in either blood or urine following maltose feeds. This is in sharp contrast to the frequency with which the other disaccharides, lactose and sucrose, were found in the urine after feedings with these sugars. I have no satisfactory explanation to offer. It is possible that the maltase secreted by the small bowel may be more efficient than sucrase and lactase, resulting in complete hydrolysis of the maltose into its component glucose molecules. Alternatively it has been suggested that blood may contain some maltase (Long, 1947) so that any of the sugar which escapes hydrolysis in the gut may be split after absorption. It is hoped to conduct further observations upon this subject.

In view of the frequent finding of sucrose, fructose,

lactose and galactose in the urines after sugar feeds it is surprising that sugars were not demonstrated more often in the blood. In fact, galactose was not observed in any of the blood samples obtained from 18 babies and 18 older children who were given lactose feeds and lactose was only found on one occasion. Sucrose was not found in the blood of any of the newborn babies who were given this sugar, although sucrosuria occurred in five (Table 2). Of 22 older children who were given sucrose, sucrose and fructose were found in the blood of four. Unfortunately urines were not collected from two of these four children, but in the urines of the other two, no sugar was found in one and fructose in the other. Of five children showing sucrosuria and fructosuria, fructose was found in the blood of two and no sugar other than glucose in the other three. It would be expected that an ingested sugar which has escaped metabolism in the body and been excreted in the urine would be demonstrable in the systemic blood. Conversely, sugar appearing in the peripheral blood should be found in the urine if the sugar is a 'non-threshold' substance which lactose, galactose and sucrose presumably are. The most likely cause for the discrepancy in the blood and urinary findings is that the chromatographic technique used was not sufficiently sensitive to demonstrate low concentrations of sugars in the blood. However, any galactose in the blood of those children who were given lactose feedings must have been present in concentrations lower than about 10 mg. per 100 ml. or it would have been detected. This is supported by the finding that only very small amounts of galactose were excreted over an eight-hour period by the five children upon whom quantitative estimations were performed (Table 8). It may be calculated that the blood levels would be less than 1 mg. per 100 ml. to give rise to this amount of galactose in the urine, assuming that galactose is a 'non-threshold' substance, even allowing for the lower renal clearance in infancy (Rubin, Bruck and Rapoport, 1949). This is in conflict with the conclusions of Hartmann, Grunwaldt and James (1953) who stated that galactose formed up to 40% of the total blood sugar in infants after milk feedings. Dormandy, Leak and Grant (1959) reached similar conclusions to those of Hartmann *et al.* (1953), although employing different analytical methods. It should be pointed out, however, that these two groups of workers only *concluded* that the bloods they examined contained large amounts of galactose because of the difference between the total sugar and the glucose. Further information has recently been obtained bearing on this subject (Haworth and Ford, 1960).

There appeared to be little correlation between the ages of the children, the dose of sugar fed to them and the subsequent frequency of sugar excretion or the concentration of the sugar in the urine. The urines from the older children, however, with one exception, contained less than 100 mg. per 100 ml. of sugar, while higher concentrations were more commonly found in the urines of the newborn babies (Table 4). This may have been because the latter babies received, on the whole, relatively higher doses of sugars than the older children, although Table 3 shows that the dose of sugar administered to the newborn babies appeared to bear no relation to sugar excretion. Sucrose was not found in any of the six urine samples obtained from children over 3 years of age, but little conclusion can be drawn from this especially since fructose and sucrose were found in the blood of an 8-year-old boy from whom, unfortunately, no urine was obtained.

Table 1 shows no significant difference in the sugar content of the urines from mature and premature babies before the test feed and Table 2 shows that premature babies excreted sugars to no greater degree than the mature babies after the sugar feed, and this in spite of the fact that on the whole they received higher doses of sugars. This is not in accord with previous findings that premature babies excreted sugars more often than mature babies (Haworth and MacDonald, 1957). Bickel (1959) also found more sugars in the urine of premature babies especially during the first 10 days of life. In retrospect there may be a valid explanation for the difference in sugar excretion rate between mature and premature babies previously found. The mature babies studied by Haworth and McCredie (1956) were fed by 'demand', and the premature babies (Haworth and MacDonald, 1957) were fed three hourly. Both groups were fed with breast milk, but it seems likely that the bigger babies may have 'demanded' feeds less often than three hourly and unfortunately no record of the times of the feeds of these babies was kept. Since the urinary sugar content has been shown to be closely related to sugar ingestion, if premature babies were fed more often than the mature, this would account for the greater number of urines containing sugar from these babies; the times of urine collection were not correlated with times of feeding.

Concerning the glycaemic response to the oral administration of lactose, sucrose and maltose in Part II (Table 7), several features are worthy of comment. Earlier workers had found that lactose ingestion caused only minimal elevation of the

blood sugar (Field, 1919; Folin and Berglund, 1922; Koehler *et al.*, 1935), but these authors were handicapped by inaccurate analytical methods. Greenwald and Pennell (1930) observed that blood sugar curves in infants following the administration of lactose and sucrose closely paralleled that following glucose administration, but the curve following dextri-maltose was lower and more prolonged. The curves shown in Fig. 1 are very different from those shown by Greenwald and Pennell and reveal a rapid rise in blood sugar after the administration of the three sugars. In the case of lactose a 'peak' value 15 minutes after administration of the sugar is shown. Following sucrose and maltose the 'peak' was at 30 minutes. The shape of a blood sugar curve is to some extent dependent upon the frequency of the blood sugar estimations, and it is very possible that the true 'peaks' of the sucrose and maltose curves might have been shown to have been between 15 and 30 minutes if more frequent blood samples had been obtained. Dodds, Fairweather, Miller and Rose (1959) recently commented upon this feature and showed that the standard method of performing a glucose tolerance test, in which samples of blood taken fasting and at 30, 60, 90 and 120 minutes, may sometimes show an abnormally flat curve when in fact a more normal type of response is demonstrated if additional samples of blood are taken between 15 and 30 minutes. Table 7 and Fig. 2 show that the blood sugar level had risen by 30% in as short a time as five minutes after the ingestion of sucrose and lactose by each group of four children. Rabinowitch (1945), Rabinowitch and Mountford (1947) and Dodds *et al.* (1959) have also demonstrated the rapid rise in blood sugar following sucrose administration and it has now been shown that an equally rapid rise of blood sugar occurs after lactose ingestion. Since sugars are not absorbed to any appreciable degree from the stomach (Long, 1947) and there is no evidence that disaccharides can be hydrolysed proximal to the small bowel, it is indeed remarkable how rapidly sucrose and lactose pass into the small intestine, are hydrolysed, absorbed and reach the systemic circulation. Unfortunately, no five- and 10-minute blood samples were obtained following maltose, although 15-minute blood sugar levels following the administration of this sugar were comparable to those following sucrose and lactose.

The only statistically significant difference between the three curves shown in Fig. 1 is that the mean 30-minute blood sugar levels following sucrose administration were greater than those following lactose. This difference was common to all age

groups studied. There are two possible explanations for this difference:

1. It might be argued that because galactose stimulates the release of insulin and fructose does not (Foa, Galansino, Costa and Pozza, 1956), the galactose released into the blood after hydrolysis of lactose had a depressant action upon the blood glucose. This is a recognized phenomenon in congenital galactosaemia in which condition high blood levels of galactose occur (Isselbacher, 1959). However, it has been shown that although some galactose must reach the systemic blood because of the frequent observance of galactosuria after lactose ingestion, the amounts were undetectable by the chromatographic method used. It is difficult to imagine that these small amounts of galactose, which must be less than 10 mg. per 100 ml. would exert an appreciable hypoglycaemic effect.
2. The method of King (1951) used for measuring total blood sugar is a 'true sugar' method but not a 'true glucose' method. Fructose was observed by paper chromatography in six of the 22 30-minute blood samples obtained from those children who ingested sucrose. Smaller amounts might have been present in more. Sucrose is not a reducing sugar and is not estimated by the King method. The 'sucrose curve' would therefore, be a measure of glucose and some fructose and the 'lactose curve' of glucose alone, since, as already stated, no other sugar was detected by chromatography in these blood samples. This seems the most reasonable explanation for the difference of the 30-minute blood levels in the two curves, although it does not explain why the 'sucrose curve' was not higher than the 'lactose curve' at other time intervals. In fact, the mean 15-minute blood sugar level of the latter curve was higher than the former although the difference is not statistically significant. This question could only be solved by repeating the experiments using the glucose oxidase method so that it would be known that only glucose and no other sugar was estimated.

It must be mentioned that these blood sugar curves should not be accepted without certain reservations. The subjects were not normal children; they were hospital patients and, although they were not suffering from any generalized acute illness at the time of the test, their glycaemic response to the

sugars may not have been normal. It has been shown that the glucose tolerance test is abnormal in the presence of infection, even skin infection (Schmidt, Eastland and Burns, 1934). However, it is doubtful whether this factor would have caused the observed difference between the sucrose and lactose curves because the two groups of children who received these sugars were fairly evenly matched as far as their original illnesses were concerned. It is also known that the preceding carbohydrate diet has a great effect upon the glucose tolerance test (Himsworth, 1935). The subjects were not taking a controlled diet before the tests were performed. They were, however, all eating the standard hospital diet well and it is likely that their preceding carbohydrate intake was fairly uniform.

Summary

Forty-seven newborn babies and 47 older children were fed with the disaccharides lactose, sucrose or maltose. Subsequent urine collection showed a high sugar excretion rate.

The source of urinary hexoses and disaccharides is undoubtedly the gut, because a sugar was not found in the urine unless a feed containing that sugar, either free or in combination, had recently been fed. Small amounts of the disaccharides, lactose and sucrose, escape hydrolysis in the gut, are absorbed unchanged and subsequently excreted in the urine.

Although earlier work had suggested that premature babies excreted sugars to a greater degree than mature babies, this was not confirmed in the present series of observations. The degree of sugar excretion did not apparently depend on the maturity or age of the child or the dose of the sugar administered by mouth.

The finding of sucrosuria in one-third of the children who were given sucrose by mouth makes it unlikely that the sucrosuria that has been described in association with mental deficiency is anything more than a coincidence.

Sucrose and/or fructose were found in the blood of six children following a feed of sucrose, but these were not the same children who excreted this combination of sugars in the urine. Lactose was found in the blood of one child following a lactose feed, but galactose was not demonstrated on any occasion. This discrepancy between blood and urinary findings was almost certainly due to technical reasons.

Maltose was not found in the blood or urine following feedings of this sugar. The reasons why this disaccharide should behave differently from lactose and sucrose have been discussed.

I wish to thank many physicians who have allowed me to examine patients under their care, and the nursing staffs of the Winnipeg Children's and General Hospitals who have helped in the collection of specimens. I am also grateful to Mr. H. Birnboim for technical assistance, Dr. R. J. Cadoret for help with the statistical evaluation and Drs. H. Medovy, B. Chown, S. Israels and K. Finkel for their advice and criticism. This work was supported by a grant from the Winnipeg Clinic Research Institute and a Mead Johnson Grant for Paediatric Research administered by the American Academy of Pediatrics.

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ADRENAL CORTICAL HYPOPLASIA IN SIBLINGS

BY

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There have been two reports recently of adreno-cortical insufficiency in infant siblings. Mitchell and Rharey (1959) reported it in two brothers, the first dying at 53 days and showing hypoplasia of the adrenal glands as the only apparent cause of death. The brother was born three years later, and exhibited a similar clinical picture of vomiting, wasting and dehydration shortly after birth. Biochemical studies were attempted but it became necessary to treat the child with adreno-cortical hormones and with sodium chloride added to his feeds. The child has remained alive to date, and it is assumed that he also suffers from adreno-cortical hypoplasia. Shepard, Landing and Mason (1959) reported adreno-cortical deficiency in two sisters. The first was well until 10 months and then developed a typical clinical picture. She died at 30 months and autopsy showed very small adrenal glands. There was no evidence of tuberculosis. The sister of this case, one of non-identical twins, developed symptoms after her first birthday; the other twin is healthy. After investigation, cortisone therapy was started and has had to be maintained, with much improvement. Neither sister exhibited a craving for salt and therefore the cortical deficiency is selective. This condition need not necessarily manifest itself early in childhood. The first case of Briggs, Goodwin and Wilson (1951), a boy of 12 years, had been fond of salt since infancy and clinically showed well developed Addison's disease. Radiographs showed calcification of mesenteric lymph nodes, but none in the region of the adrenal glands. Treatment with 'eucortone' at first, and later with D.C.A. pellet implants, and with sodium chloride orally, has been effective, and he was well at the time when the article was published. This boy's brother, 17 years of age, developed a more acute illness with epigastric pain, vomiting, loss of weight and increased depth of skin pigmentation. Treatment was given as for an Addisonian crisis, but he died 72 hours after admission to hospital. Necropsy revealed small adrenal glands, and histological examination showed atrophy of the cortex

of each. There was no evidence of tuberculosis. The thymus was large. Both parents were healthy and the authors suggested that a genetic factor may be involved as in thyrotoxicosis, diabetes mellitus and the Laurence-Moon-Biedl syndrome.

We report a further family showing adrenal hypoplasia. Both boys in this family died in the neonatal period and received minimal corrective treatment. Therefore, the histological appearances of their endocrine glands are unaffected by therapy.

Case Reports

In 1953, the mother became pregnant for the first time, but had a spontaneous miscarriage at 4½ months. The cases reported were the result of second and third pregnancies.

Case 1. This male infant was born in hospital on May 4, 1955, as a spontaneous vertex delivery at full term after a normal pregnancy. The birth weight was 7 lb. 12 oz. (3.52 kg.). 'Physiological' jaundice appeared for a few days. Before dismissal, there had been occasional vomiting after breast feeding, but the condition subsided. The baby was well for his first four days at home, and then his condition deteriorated, and he was admitted to the Royal Hospital for Sick Children, Glasgow, on May 17, 1955. On that day his motions were green and very loose.

He was dehydrated, with poor muscle tone, although he was 113% of his expected weight. Lumbar puncture gave a clear cerebrospinal fluid. Rectal swabs revealed no pathogenic organisms. Four days later his general condition was improved but he remained rather listless. On May 23, 1955, he collapsed suddenly with copious green vomitus. 'Eucortone' 0.5 ml. was given every four hours. Surgical opinion was sought, and at laparotomy a volvulus was found involving the caecum and ascending colon. This was reduced and an obstructing band was divided. 140 ml. of quarter-strength normal saline with 5% glucose was given intravenously over the next six hours. Oral fluids were started four hours postoperatively and 'eucortone' was stopped on the fifth postoperative day. His condition improved over seven postoperative days, but on the eighth day (June 1, 1955) he went off his feeds once more, became marasmic and he died on June 2, 1955, at 4 weeks of age.

At necropsy the child weighed 5 lb. 10 oz. (2.55 kg.).

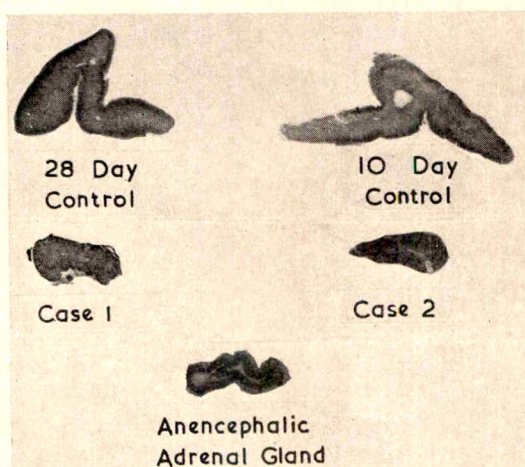


FIG. 1.—Specimens of adrenal glands of Cases 1 and 2 compared with normal controls for these ages and with an anencephalic adrenal gland. ($\times 5/3$.)

The abdominal surgical wound was healthy. The alimentary tract, liver (120 g.), pancreas and spleen (6 g.) were normal. The respiratory passages contained terminal bile-stained inhaled vomitus and the lungs showed mild patchy collapse. The heart (17 g.), great vessels, genito-urinary and central nervous systems were normal. The ductus arteriosus was widely patent. Both adrenal glands were exceedingly small (Fig. 1) and together they weighed 0.65 g. No accessory adrenal tissue was found in the para-aortic area, pelvis or in relation to the testes which were fully descended.

The histological features will be considered later.

Case 2. In 1958 the mother became pregnant for the third time and suffered from no infection during this period; neither were radiographs taken. The child, a male, was born at home on October 7, 1958, and weighed 8 lb. (3.63 kg.). Progress was steady for a week, but on October 15, 1958, he vomited his feeds. On October 16 he refused his feeds and was cold, listless and grey. He continued to vomit and was admitted during the night to the Royal Hospital for Sick Children, Glasgow. His parents gave the history of a child who had died three years previously 'as a result of a twisted bowel'. Unfortunately, they were unaware of the additional condition found at necropsy, and in view of the urgency of treatment because of this present child's moribund condition, the clinicians involved did not consult the previous child's case records until later. In retrospect, this was perhaps unfortunate.

Examination, the child being 9 days old, showed him to be 95% of his expected weight, listless, grey, dehydrated and with a subnormal temperature. Lumbar puncture revealed a clear cerebrospinal fluid and the W.B.C. count was 10,800/c.mm. Blood was taken for culture, but only a contaminant grew. On the assumption that the child had an overwhelming infection, an intravenous

infusion of quarter-strength normal saline with 5% glucose was set up. 100 mg. of hydrocortisone were placed in the contents of the first bottle. In addition, intramuscular hydrocortisone injections of 25 mg., and intramuscular tetracycline 25 mg. were given every six hours. The child died eight hours after admission.

At necropsy the child weighed 7 lb. 3 oz. (3.26 kg.). There was no abnormality of the respiratory passages, lungs, heart (29 g.), great vessels, the alimentary tract, liver (150 g.), pancreas, spleen (6 g.), the genito-urinary or central nervous systems. The only abnormality was the presence of unusually small adrenal glands. Together they weighed 0.9 g. (Fig. 1), and no adrenal tissue was found at any other site.

There was no family history of adrenal cortical hypofunction either in the grandparents, the parents or in their sibs.

Histological Features. The histological details of the two cases are similar and are considered together.

ADRENAL GLANDS. Sudanophilic material is present in the zona reticularis of the adult cortex and in individual cells of the almost completely involuted foetal zone (Fig. 2). The features are the same in both cases, and are accompanied by cytomegaly in the foetal zone. The columns of the zona fasciculata are not normal for a resting gland (Fig. 3). Fig. 4 shows that there is barely any zona glomerulosa, and the cells of the zona fasciculata show much variability in size, and in nuclear and cytoplasmic staining properties. There is no evidence of the more insidious cytolytic necrosis seen in adult cases of Addison's disease (Cooke and Russell, 1935).

Professor T. Symington, Department of Pathology, Royal Infirmary, Glasgow, has examined one gland from each case by histological and by histochemical methods, and reports that both glands have been very active, and that he is unable to find any abnormality of function by these investigations.

Normal medullary tissue is present, but it is difficult to assess whether or not this is present in normal amount.

THE PITUITARY GLAND. The glands were normally situated in both cases. Gomori's aldehyde-fuchsin method (Gomori, 1950) shows that basophil cells are present in increased numbers in both glands (Fig. 5). This finding has been confirmed by Lieb's phosphotungstic acid haematoxylin (Lieb, 1948), and modified trichrome and P.A.S. methods. Normally, basophils are present singly or in clumps of two or three cells. Fig. 5 shows marked hyperplasia in both cases, and, if anything, a tendency to become nodular in Case 1, which survived the longer.

Thus, adrenal hypoplasia is the primary defect and not the result of pituitary hypofunction in both of these children. Conclusive evidence is obtained from histological study of the other endocrine organs.

THE THYROID GLAND. The thyroid gland in Case 2, who lived for 10 days, shows no abnormality (Fig. 6b). The gland of Case 1 who lived for four weeks, shows collapsed acini devoid of colloid (Fig. 6a), an appearance

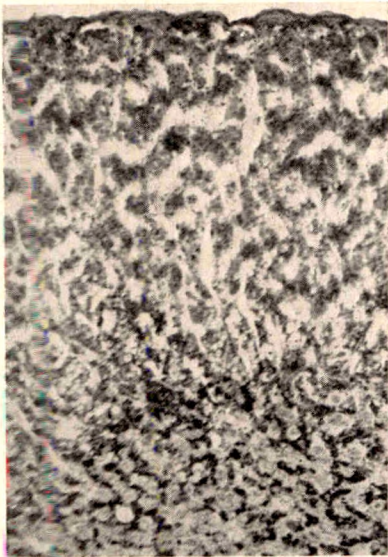


FIG. 2a.

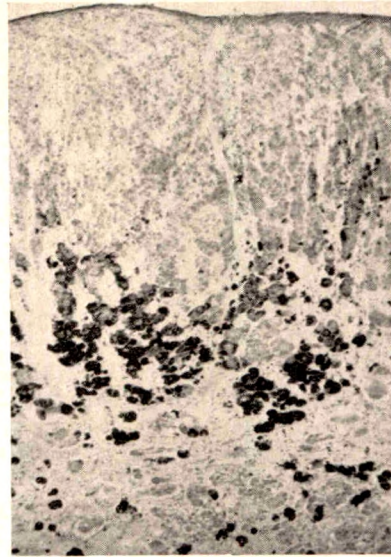


FIG. 2b.

FIG. 2.—Low power view of adrenal glands of Case 1, (a), and of Case 2, (b), stained with Sudan III and IV. The difference in quality of the two photographs is due to the gland of Case 1 being embedded in gelatin. ($\times 60$.)

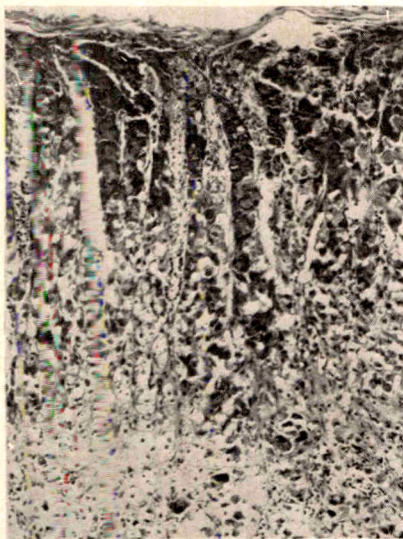


FIG. 3a.

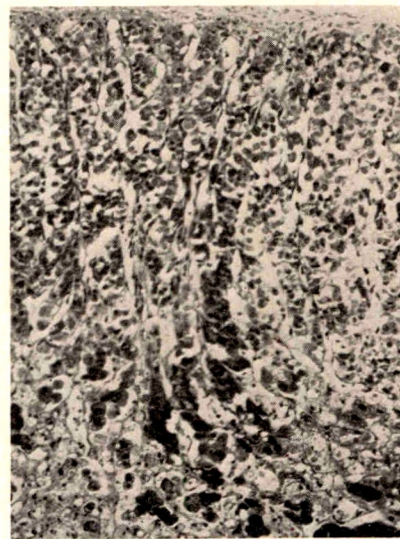


FIG. 3b.

FIG. 3.—Low power view of adrenal cortex of Case 1, (a), and of Case 2, (b), showing disorganization of cortical structure. (Masson's trichrome $\times 100$.)

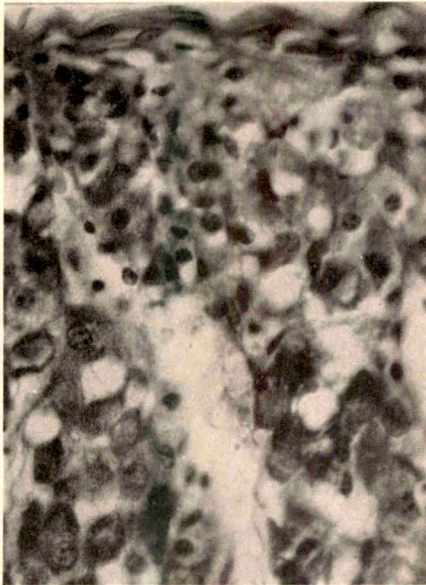


FIG. 4a.

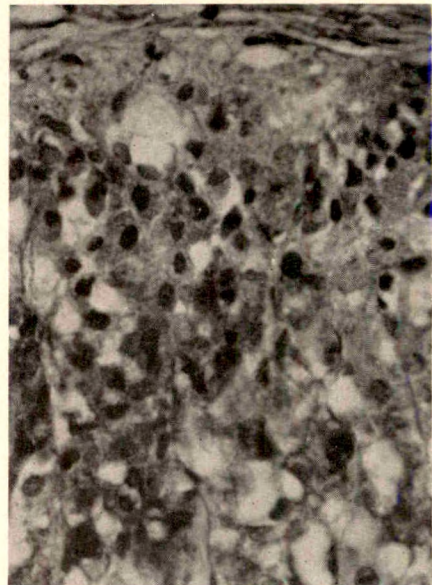


FIG. 4b.

FIG. 4.—High power view of adrenal cortex of Case 1, (a), and of Case 2, (b), showing poor zona glomerulosa and moderate pleomorphism of cells of zona fasciculata. (Masson's trichrome $\times 413$.)

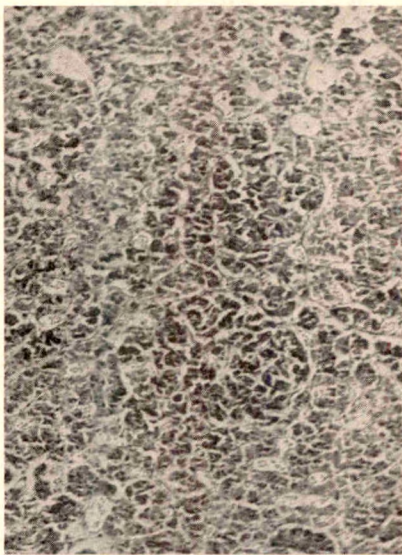


FIG. 5a.

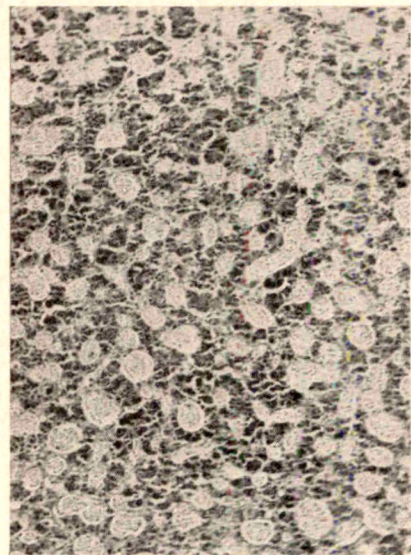


FIG. 5b.

FIG. 5.—Pituitary gland of Case 1, (a), and of Case 2, (b). The basophil cells are dark. (Gomori's aldehyde fuchsin $\times 100$.)

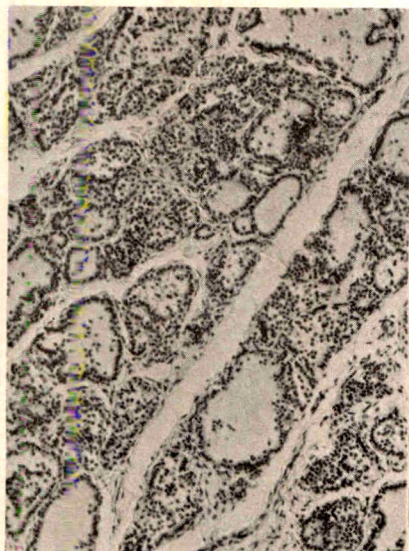


FIG. 6a.

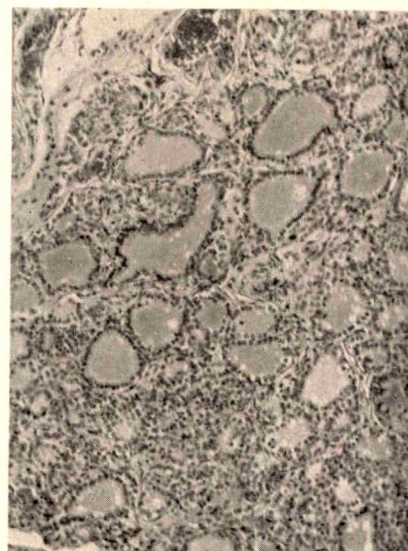


FIG. 6b.

FIG. 6.—Thyroid gland of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows a thyrotrophic hormone-like effect. (Haematoxylin and Eosin $\times 100$.)

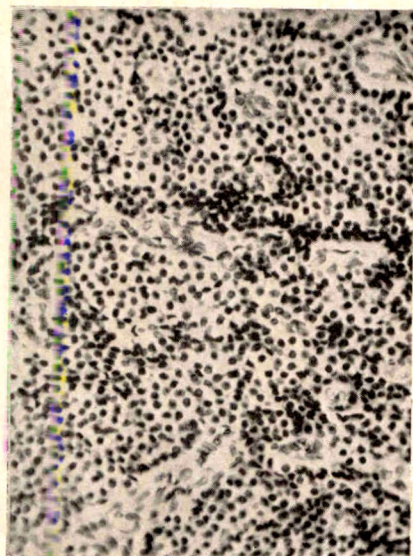


FIG. 7a.

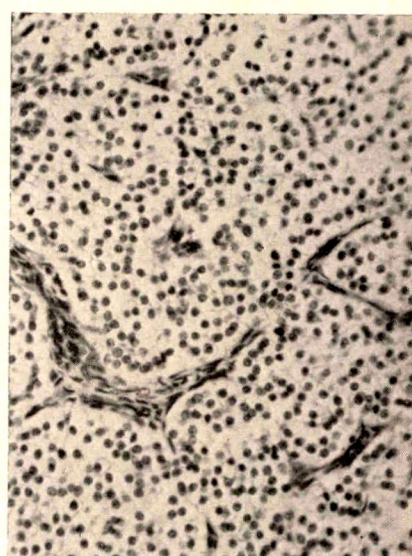


FIG. 7b.

FIG. 7.—Parathyroid gland of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows some upset which is difficult to interpret. (Haematoxylin and Eosin $\times 100$.)

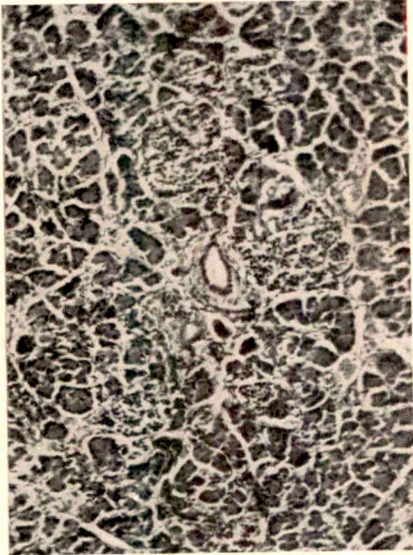


FIG. 8a.

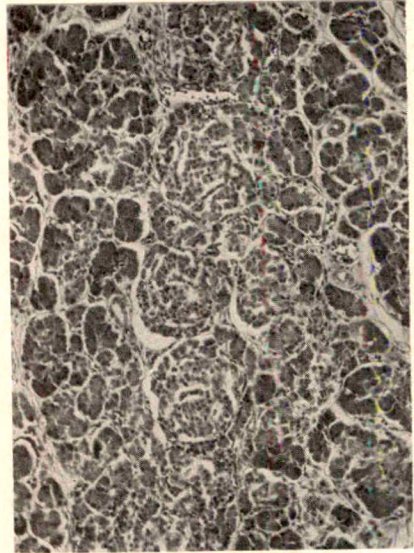


FIG. 8b.

FIG. 8.—Pancreas of Case 1, (a), and of Case 2, (b). Both are normal. (Haematoxylin and Eosin $\times 100$.)

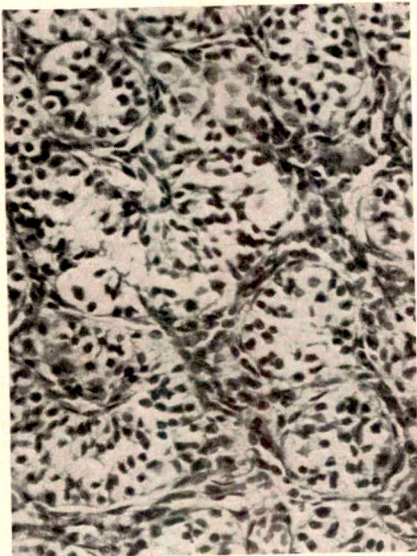


FIG. 9a.

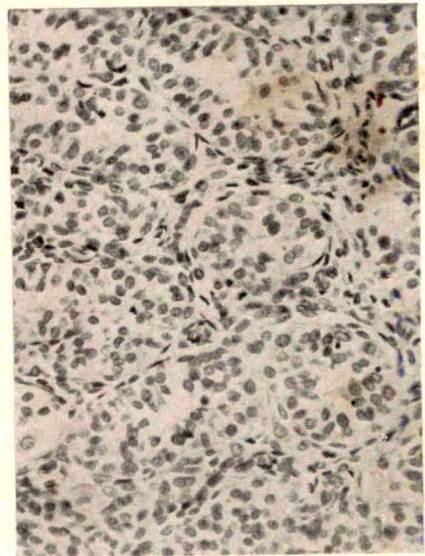


FIG. 9b.

FIG. 9.—Testis of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows tubular atrophy with reduced spermatogenic activity. There is no detectable abnormality of the interstitial cells in either case. (Haematoxylin and Eosin $\times 100$.)

which may result from over-production of thyrotrophic hormone (Sclare, 1956).

THE PARATHYROID GLANDS. In neither case do the glands appear to be unusually large or small. The gland of the shorter lived infant (Case 2) shows no histological abnormality (Fig. 7b). The gland of Case 1, however, shows an increased number of smaller cells with more hyperchromatic (or pyknotic) nuclei (Fig. 7a). We find it impossible to conclude from this whether the gland is undergoing atrophy or hyperplasia. In favour of atrophy is the apparent increase in condensation of blood vessels per field. On the other hand, Greene (1948) cites experimental evidence in favour of a parathyrotrophic hormone. Study of a section of rib from each case fails to demonstrate bone absorption, and a section of kidney from each case fails to show evidence of nephrocalcinosis by Von Kossa's stain. It may be that neither infant lived long enough to exhibit these changes.

THE ISLETS OF THE PANCREAS. Islet tissue appears to be present in normal amount (Fig. 8) and α and β cells are present in both cases.

THE TESTIS. The testis of Case 2 shows a normal degree of spermatogenesis (Fig. 9b). The testis of Case 1 shows a relative degree of atrophy of the seminiferous tubules (Fig. 9a) with markedly reduced spermatogenic activity, although artefact is present as a result of unsatisfactory fixation. This finding is consistent with the records of testicular atrophy in pituitary basophilism in the adult. Interstitial cells appear to be present in normal numbers in each case.

THE THYMUS. This organ is generally considered to be an endocrine gland, although in hypofunction of the adrenal cortex it appears to behave in the same manner as lymphoid tissue elsewhere in the body (Cooke and Russell, 1955). In the present two cases, the weight of the thymus was at the upper end of the scale of normal limits, and it must be assumed that the episode of adrenal hypofunction was too acute to allow time for the glands to show hyperplasia, regeneration or a reduced rate of involution.

Discussion

Hypoplasia of the adrenal glands is well known in association with anencephaly (Angevine, 1938) and in association occasionally with other congenital deformities of the central nervous system. In another group, however, adrenal hypoplasia is the only abnormality (Šikl, 1948; Deamer and Silver, 1950; Geppert, Spencer and Richmond, 1950; Proenzano, 1950; Welsh and Mehlin, 1954; Williams and Robinson, 1956; Harlem and Myhre, 1957; and MacMahon, Wagner and Weiner, 1957), and some of these cases have responded well to hormone therapy (e.g. Case 1 of Williams and Robinson, 1956). Some authors emphasized that the survival of these children was precarious, with

sudden irrecoverable collapse if therapy were stopped even for a short period, and for this reason Mitchell and Rhaney (1959) felt that it was unjustified to investigate their second case fully while denying the infant the chance of recovery with replacement therapy. The histological appearances of the adrenal cortex of the brothers reported here resemble very closely those of Case 1 of Mitchell and Rhaney (1959) even to the presence of cytomegaly (Kampmeier, 1927; Beatty and Hawes, 1955). It should be stated that we are aware of endocrine gland involution during replacement therapy, but that we do not consider this process to be important in our cases, nor in the similar cases reviewed by us, because the adrenal glands are hyperactive. We believe that their small size is a congenital anomaly. It is essential in such cases, however, to make a thorough study of the whole endocrine system.

For example, Blizzard and Alberts (1956), Brewer (1957) and Ehrlich (1957) have described congenital aplasia or hypoplasia of the pituitary gland, and Mosier (1956) has recorded the condition, which is accompanied by hypoplasia of the adrenal glands, in siblings.

Further, our study of the literature reveals several familial syndromes which involve adrenal gland hypofunction: (1) The syndrome of hypoparathyroidism, adreno-cortical insufficiency and chronic moniliasis brought to general notice by Sutphin, Albright and McCune (1943) and followed by several reports, all from America (Leonard, 1946; Collins-Williams, 1950; Leifer and Hollander, 1953; Baker, 1954; Papadatos and Klein, 1954; Craig, Schiff and Boone, 1955; Whitaker, Landing, Esselborn and Williams, 1956; and DiGeorge and Paschkis, 1957); (2) the association of Addison's disease with thyroid gland changes in some instances (Wells, 1930; Anderson, Goudie, Gray and Timbury, 1957), and the well-known familial tendency to hyperthyroidism (Martin and Fisher, 1945), or to hypothyroidism as in sporadic non-endemic goitrous cretinism (Hutchison and McGirr, 1956), make a study of the thyroid gland essential; (3) the coincidence of diabetes mellitus and Addison's disease was described by Bloomfield (1939) and by McNicol and McNicol (1960) and since a familial tendency in diabetes is now well known, a familial tendency to both conditions simultaneously may be reported in the future; and (4) the syndrome of Addison's disease in association with familial spastic paraplegia has been recorded recently by Harris-Jones and Nixon (1955).

The existence of these conditions makes it necessary to examine not only these endocrine organs, but to examine the gonads histologically

in order to exclude the presence of ectopic adrenal tissue at this site, and also to examine the central nervous system, mainly to exclude a congenital abnormality of the fore-brain. We were unaware of the existence of the association between Addison's disease and familial spastic paraplegia and therefore a histological examination of the spinal cord was not made.

The findings suggest that our cases exhibit primary adrenal gland hypoplasia with secondary pituitary basophilism, although it is not possible to state categorically that the infants would not have developed later one or other of the syndromes referred to above, had they survived.

Summary

Congenital adrenal hypoplasia is recorded in two brothers who died in the neonatal period.

Two previous examples of this condition in infants have been reported; one sibling has been maintained alive by replacement therapy in each.

Histological study suggests that the present two cases suffered from primary adrenal gland hypoplasia with secondary pituitary basophilism, the effects of which are demonstrable on the other endocrine glands.

We are very grateful to Dr. J. H. Hutchison for permission to abstract the case records of these two cases, to Professor S. Graham for advice, and to Professor T. Symington for studying an adrenal gland from each case.

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POSTURAL TREATMENT OF CHILDREN WITH A PARTIAL THORACIC STOMACH ('HIATUS HERNIA')

BY

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Considerable debate centres round the best way of treating children affected with a small partial thoracic stomach ('hiatus hernia' or 'short oesophagus') uncomplicated by an oesophageal stricture. Two diametrically opposed views exist. On the one hand there are those workers who subscribe to a conservative regimen of management. Others, in the belief that the disorder is analogous to the hiatus hernia of adults, advocate surgical procedures aimed primarily at replacing and retaining the stomach wholly within the abdomen.

The following report records the long-term results achieved with conservative postural methods of treatment. The value of such therapy has been assessed by comparing the progress of treated children with the expected outcome as deduced from the natural history of the disorder (Carré, 1959). The treatment of children with a partial thoracic stomach complicated by an oesophageal stricture is not considered.

Method

Definition of Abnormality. The following review is restricted to patients shown radiologically to have part of the stomach protruding through the oesophageal hiatus. In every instance the gastro-oesophageal junction has been situated within the thorax at the upper limit of the intrathoracic gastric loculus. Patients with only gastro-oesophageal incompetence have not been considered.

Assessment of Clinical Progress. Clinical progress has been determined objectively. The same classification of symptoms has been employed as used in the study of the natural history (Carré, 1959), namely:

Frequent: If vomiting and/or difficulty in swallowing solid food was noted to occur daily or at least on alternate days in children taking a normal diet for age. The routine use of a mashed diet occasioned by a child's difficulty in swallowing solids has been

interpreted as implying the existence of frequent symptoms despite the fact that the child on its mashed diet might have been having little or no vomiting or dysphagia.

Moderate: If vomiting and/or difficulty in swallowing solid food was noted to occur on an average of less than three times weekly but at least monthly in a child taking a normal diet for age.

Minimal: If vomiting and/or dysphagia were absent or occurred on average less than once a month in a child taking a normal diet for age.

Type of Patient Considered. In the study of the natural history (Carré, 1959) it was concluded that untreated clinically affected patients could be divided into the following relatively distinct clinical groups:

Group	Change in Symptomatology on Weaning to Mixed Diet	Prognosis	Clinically Affected Patients (%)
Survivors	I No symptoms or improved	Benign course. Majority free of symptoms by 2 years.	60-65
	II No improvement or worse	(a) Prolonged clinical course with 'moderate' or 'frequent' vomiting and / or dysphagia commonly persisting to at least 4 years of age; no oesophageal stricture; (b) Symptomatology and progress dependent on presence of an oesophageal stricture	30 5
Deaths		In the absence of an oesophageal stricture death likely to occur during infancy from combination of marasmus, biochemical disturbances and infection	<5

Because of the naturally occurring variation in clinical progress exhibited by individual patients, consideration of results has been restricted to the following two groups of patients whose progress in the absence of treatment could be forecast reliably.

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GROUP A. All patients in whom a partial thoracic stomach had been radiologically confirmed by 3 months of age were included. Since clinically affected children progress in a similar manner during the early weeks of life irrespective of the eventual outcome (Carré, 1957), it is apparent that all clinical types would be correctly represented in such a group. Thus, in the absence of beneficial treatment about one-third of these patients would be likely to pursue a protracted clinical course (Groups IIa and b of Natural History Study: Carré, 1959).

GROUP B. This group comprised patients who were between 6 months and 2 years of age when started on postural treatment and who were not improved clinically when weaned on to a solid diet; no patient had a proven oesophageal stricture when first seen. (Group II patients of Natural History Study: Carré, 1959.) In the absence of beneficial therapy almost all these children could therefore expect to suffer from troublesome symptoms until at least 4 years of age with about one in six developing an oesophageal stricture.

Group A Patients

During the period of study all infant patients whose partial thoracic stomach had been radio-

logically confirmed by 3 months of age were treated routinely by posture from the time of diagnosis; none of these patients received any form of surgical treatment before the age of $3\frac{1}{2}$ years. In view of the therapeutic policy adopted this group therefore represents a consecutive and unselected series of patients all of whom were started on postural treatment within the first 3 months of life. All surviving patients have been followed up to at least 4 years of age.

Although some patients had oesophageal narrowing on fluoroscopy, none had a proven oesophageal stricture at the time of starting treatment. All suffered from symptoms of 'frequent' severity when started on treatment. No child showed signs of a commencing spontaneous symptomatic improvement.

Patients given 'Adequate' Postural Therapy. In this section only those patients have been considered whose treatment fulfilled the following requirements: (a) Patients were kept in a sitting posture with the trunk inclined at 60° or more with the horizontal. Posturing of a lesser degree occasionally employed during the early stages of this study was found to be therapeutically ineffective (Fig. 1). As it was impossible to maintain this degree of propping

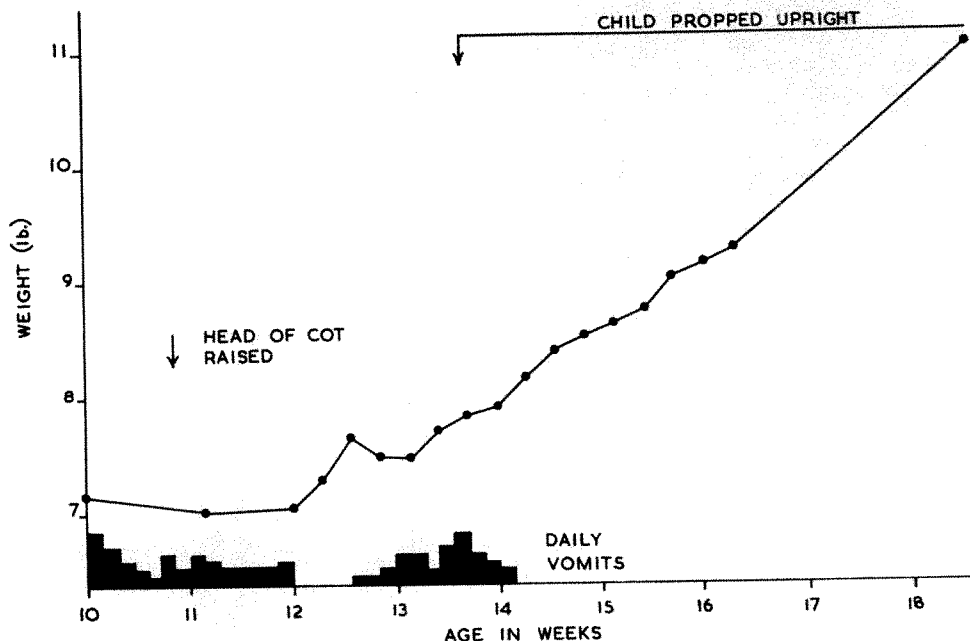


FIG. 1.—At 10 weeks this infant weighed only 10 oz. more than his birth weight. The patient was treated by propping with one pillow and raising the head of the cot on 10-in. blocks. No significant improvement was noted over a period of three weeks. Subsequent to nursing in an erect posture vomiting ceased and a rapid gain in weight was recorded. This patient was $7\frac{1}{2}$ years old when last seen. There had been no recurrence of vomiting.

TABLE 1
PROGRESS OF 34 PATIENTS STARTED ON 'ADEQUATE' POSTURAL TREATMENT BEFORE 3 MONTHS OF AGE

Case No.	*Adequate Postural Treatment		Supplementary Treatment	Clinical Progress			Age at Last Review	
	Age Started (weeks)	Age Discontinued (months)		Severity of Symptoms and Age			Yrs	Mths
				Frequent	Moderate	Minimal		
16	1	12	—	B - 1w	—	1w -LR	7	5
30*	7	30	—	B -LR	—	—	6	8
31	2	10	—	B - 2w	—	2w -LR	7	0
33	2	14	Thickened feeds	B - 2w	—	2w -LR	6	5
37	12	12	Thickened feeds	5w- 4½m	—	4½m -LR	5	6
38	2	8	—	B - 4w	4w- 7w	7w -LR	4	0
30	6	9	—	B - 6w	—	6w -LR	5	9
31	2	7	Alkali	B - 2w	2w- 5m	5m -LR	6	7
37	2	20	—	B - 2w	2w- 8w	8w -LR	7	1
38	12	12	—	B - 3m	3m- 4m	4m -LR	7	6
39	2	8	—	B - 2w	2w- 6w	6w -LR	4	11
102	2	14	—	B - 2w	2w-12m	12m -LR	5	6
103	3	4	—	B - 3w	3w- 5w	5w -LR	6	1
106†	2	18	Atropine, alkali	B - 3m	3m- 4y	—	7	1
				4y -LR	—	—	6	3
112	10	7	—	B - 5m	—	5m -LR	4	0
113	2	6	—	B - 2w	2w- 4w	4w -LR	6	5
114	6	21	—	B - 6w	6w- 5m	5m -LR	5	10
					8m-12m	12m -LR	6	0
115	3	16	—	B - 3w	—	3w -LR	5	11
121	2	15	—	B - 2w	2w- 4w	4w -LR	4	5
123	4	12	Alkali, thickened feeds	B - 2m	2m- 5m	5m -LR	5	3
124	9 days	3	—	B - 2w	2w- 6w	6w -LR	4	1
126	7	16	Thickened feeds	B - 8w	—	8w -LR	6	0
127	12	23	Thickened feeds	B - 6m	6m-13m	13m -LR	7	4
			Alkali, atropine	—	—	—	5	3
139	9 days	2	—	B - 2w	—	2w -LR	5	1
144	9 days	6	—	B - 2w	—	2w -LR	5	4
146	12	24	Thickened feeds	B - 5m	5m-20m	20m -LR	4	5
147	2	6	—	1w- 3w	3w- 3m	3m -LR	5	0
148	4	6	—	B - 5w	5w- 3m	3m -LR	5	3
149	12	14	—	1w-14w	—	14w -LR	4	9
154	3	9	—	B - 6w	6w-12w	12w -LR	4	7
156	2	12	—	B - 4w	4w- 9m	9m -LR	4	1
158	7	5	—	5w- 9w	9w- 3m	3m -LR	4	1
159	4	10	Thickened feeds, atropine	B - 7m	7m- 8m	8m -LR	5	3
			Thickened feeds	B - 3w	3w- 7w	7w -LR	5	3

* Only two vomits per year from 2 years, but food finely cut up because of dysphagia.

† Developed an oesophageal stricture; surgical repair of 'hiatus hernia' when 6 years old.

Abbreviations: d = days w = weeks m = months y = years LR = last review B = birth

without the use of some form of chair or supportive harness only those infants have been included who were kept propped up by means of some such appliance.* (b) Posturing was maintained continuously day and night up to the age of 1 year, or if symptoms had subsided before, until a minimum of six weeks complete freedom of symptoms had been recorded.

Treatment Given in Addition to Posture. The routine policy throughout was first to try the effect of posture without altering the feeding regimen in any way. If progress was considered unsatisfactory postural treatment was augmented by thickening

the feeds.† In fact, only eight of 34 infants were given thickened feeds in addition to postural therapy. Treatment was further supplemented in two of these eight by the administration of alkali which was also prescribed for two others in the group.

Results. Thirty-four infants were treated by adequate sustained posture as defined above. All were kept under regular out-patient supervision at a special follow-up clinic throughout the period of treatment. The clinical progress of these infants is summarized in Table 1.

† *Methods used to thicken feeds:*

- Benger's Food—one teaspoonful to 2 oz. of milk feed.
- Cornflour—one tablespoonful to a pint of milk feed.
- Carob-seed flour, marketed under the name of 'nestargel' by the Nestlé Company—half to one teaspoonful to 12 oz. of feed (0.5-1% of powder to each feed).

These thickened feeds were given by feeding bottle using a teat with a large hole. Additional thickening, if desired, was obtained by merely increasing the concentration of the thickening agent.

* Initially many methods were devised, but the plaster chair described by Hill (1953) has been used routinely in the treatment of patients during the latter part of this study. Other postural appliances have been described by Davies (1952) and Rosenweig (1954).

Only four of these 34 infants suffered from either 'moderate' or 'frequent' symptoms beyond 12 months and only two beyond 2 years of age. One of these latter children (Case 80) had vomited only two to three times a year from 2 years of age until last seen when 6 years 8 months old. During this period, however, she had continued to have difficulty with swallowing and required to have solid food finely cut up. Examination by barium swallow and fluoroscopy at her last attendance showed no evidence of oesophageal narrowing. The other child (Case 106) showed no improvement with treatment and developed an oesophageal stricture. A surgical repair of the 'hiatus hernia' when she was 6 years old did not produce any significant benefit and when seen one year later she still complained of frequent dysphagia and vomiting.

These results compare favourably with the expected outcome of a similar group of untreated patients (Carré, 1959). Without treatment, it is probable that at 12 months of age about 22 and at 2 years about 15 patients would have been troubled with symptoms of either 'moderate' or 'frequent' severity. Of these, 11 would still have been vomiting more than once a month on average at 4 years with

one or two having developed an oesophageal stricture. One other patient might have died in infancy.

The speed of response to treatment was variable. In some patients improvement was dramatic while symptoms in others abated only slowly over a period of months. The speed of response may be determined from the time interval between the institution of therapy and the onset of symptoms of 'minimal' severity. This period was less than two weeks in 12 patients. In a further 12 this interval varied between two weeks and three months. In eight patients the response to treatment was gradual with intervals varying from three to 17 months between the commencement of treatment and the onset of 'minimal' symptoms. Two patients failed to respond. Confirmatory observations were recorded in 20 other similarly treated patients excluded from the present review because of an inadequate follow-up. Seven of these 20 patients had virtually ceased vomiting within two weeks and another eight within three months of starting treatment. The prompt beneficial response which may follow the institution of postural treatment is illustrated by Case 121 (Fig. 2).

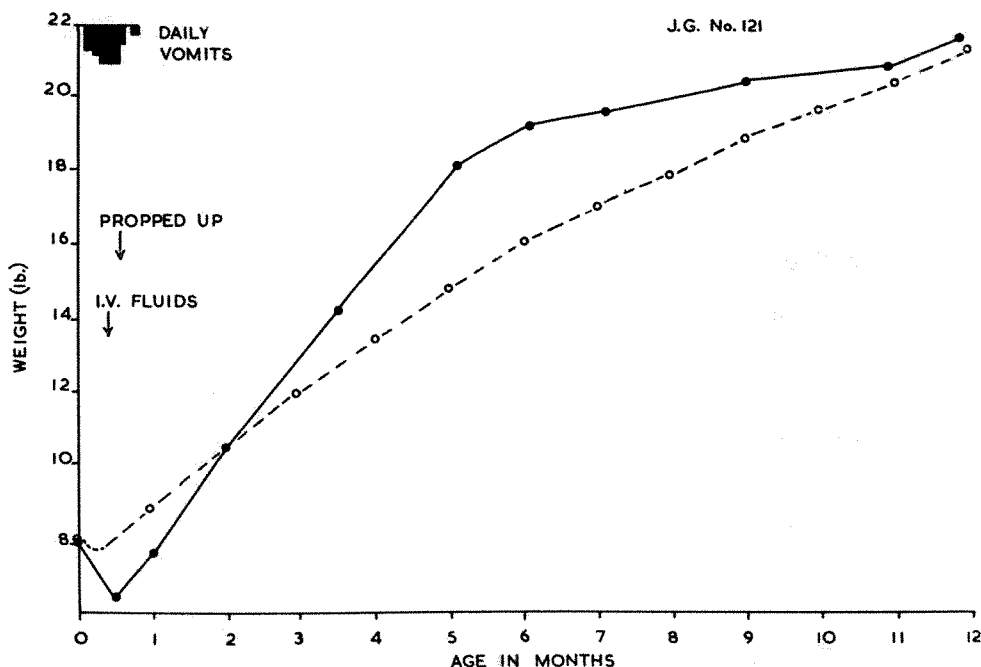


FIG. 2.—The progress of this child illustrates the prompt symptomatic response which may follow the institution of adequate postural treatment in early infancy. This infant commenced vomiting at 3 days. When 2 weeks old she weighed 1 lb. 12 oz. less than her birth weight. Following rehydration with intravenous fluids and treatment by nursing in an erect posture vomiting ceased dramatically and concurrently her weight rose steadily. She was last seen at 6 years of age; there had been no recurrence of symptoms, but she still had a demonstrable partial thoracic stomach when examined by barium swallow and fluoroscopy. Weight ———; expected weight gain - - - - -

TABLE 2
PROGRESS OF 15 PATIENTS DIAGNOSED BEFORE 3 MONTHS OF AGE BUT GIVEN
'INADEQUATE' POSTURAL TREATMENT

Case No.	Postural Treatment		Supple- mentary Treatment	Clinical Progress			Age at Last Review	Remarks
	Age Started (weeks)	Age Discontinued (months)		Severity of Symptoms and Age				
				Frequent	Moderate	Minimal	Yrs Mths	
21	2	5	Thickened feeds	2d - 4 m	4 m-11 m	11 m-LR	7 5	Propped with pillows only
24	2	3	Thickened feeds	B -4½ m	—	—	4½ m (died)	Propped for ½ hour after feeds
25	6	2	—	B -10 w	—	—	10 w (died)	Adequately propped for ½ hour after feeds
92	14 mths	7 24	Thickened feeds, alkali, atropine	4 w- 8 m 12 m-3 y 7 m	8 m-12 m —	3 y 7 m-LR	4 2	Pneumonia 11 and 19 mths; adequate propping 6 wks- 7 mths; one pillow only used 14 mths-2 yrs; resection of oesophageal stricture and partial gastrectomy at 3 yrs 7 mths
107	8	8	Thickened feeds	B - 3 m	3 m-15 m	15 m-LR	6 7	Two pillows only
111	1½	1	Atropine	B - 3 w	3 w- 8 w	8 w-LR	7 4	Adequately postured 2-4 wks only
122	1½	20	Alkali, thickened feeds	B - 6 m	6 m-LR	—	6 3	Propped with pillows only
130	6	30	—	7 d- 5 m	5 m-17 m	17 m-LR	6 1	One pillow and head of cot raised
140	2	3	Atropine, thick- ened feeds	B - 8 w 4 m- 7 m	8 w- 4 m 7 m-12 m	12 m-LR	5 3	Adequately propped, but for insufficient period
143	6)(6	9	—	—	B - 4 m	4 m-LR	5 0	Pillows only
145	6)(6	9	—	B - 3 w	—	3 w-LR	4 6	Adequately propped 2-4 wks only, then one pillow to 9 mths
150	6	5	—	2 w- 6 w	6 w-3½ y	3½ y-LR	4 5	Propping adequate, but for insufficient period
153	1½	24	—	B - 4 m	4 m-2½ y	2½ y-LR	4 5	Head of cot raised and one pillow
164	6	18	—	2 w- 5 m	5 m-12 m	12 m-LR	4 0	Adequate propping 6-12 wks only
165	12	12	Thickened feeds, alkali	B -12 m	12 m- 3 y	3 y-LR	4 3	Pillows only and for one hour after meals

Abbreviations as in Table 1.

Patients Given 'Inadequate' Postural Treatment.

For the purpose of comparison a summary is included of the progress of 15 children given 'inadequate' treatment. Postural treatment has been judged as 'inadequate' for the following reasons. Pillows only were used to posture seven patients, while in eight instances propping though adequate in degree, was either employed intermittently or continued for an insufficient period (Table 2).

There was an additional important difference between the two groups. These patients, in contrast to those already discussed, were not kept under regular out-patient supervision. In other respects they were exactly comparable to those considered in the previous section with the exception that one patient (Case 143) had symptoms of only 'moderate' severity at the time of commencing treatment.

Results. Eight children were well by 2 years. Two patients died in early infancy. One child developed an oesophageal stricture. The remaining four children suffered from symptoms of 'moderate' severity beyond 2 years of age; one of these still had 'moderate' symptoms at 4 years.

These results are not dissimilar to the expected outcome should none of these children have been treated by posture. For, in the absence of treatment eight or nine would probably have been well by 2 years of age. Of the others, possibly one might have died and another developed an oesophageal stricture. The remaining four or five children would probably have suffered from symptoms of at least 'moderate' severity up to 4 years of age and longer.

Group B

The greater strength and activity of these older patients made it infinitely less practical to effect a comparable degree of sustained propping as quoted for Group A patients. It has been necessary, therefore, to adopt much less strict criteria of treatment. Patients have been included where a genuine attempt had been made to keep them propped throughout the night and during daytime rest periods.

Children considered in this survey have been treated by posture for either a minimum period of nine months, or a period extending for six weeks beyond the onset of 'minimal' symptoms should

this have occurred before nine months treatment had been given.

No child was subjected to any surgical procedure other than oesophagoscopy during the nine months of postural treatment.

All patients considered were 4 years of age or more at the time of their last review.

Results. There were only nine patients whose symptomatology and treatment conformed with the above conditions. Alkali was given as supplementary treatment to five patients; two of these were given atropine as well. The clinical progress of these patients is summarized in Table 3.

Three patients developed an oesophageal stricture; one other child suffered from symptoms of 'moderate' severity until the age of 6 years 11 months. The remaining five children had only 'minimal' symptoms at 4 years of age; in four 'minimal' symptoms had dated from 2 years or younger. If untreated it is probable that only one or two of the nine patients would have shown much improvement by 4 years of age.

The response to treatment appeared to be unrelated to the age of commencing treatment. Of four whose treatment started before 12 months of age, two developed an oesophageal stricture while two were well at 4 years; of five commencing treatment between 12 and 24 months, one developed a stricture, one suffered from 'moderate' symptoms until almost 7 years and three were clinically well at 4 years.

Fig. 3 shows the progress of one patient who responded to conservative therapy.

Complications of Postural Treatment

The only complications observed which could in any way be attributed to postural therapy were occasional sore buttocks, usually encountered at the start of treatment, and a flattening of the head similar to that described by Craig (1953).

Flattening of Head. The following brief review was undertaken with the object of determining more precisely the relationship of a flattened head to postural treatment. In the absence of anatomical measurements a child has been regarded as having a 'flat' head if the alteration in head shape was sufficiently obvious to cause comment. Three groups of patient are considered:

1. Children who were kept sitting up at 60° or more throughout each 24 hours for a minimum period of one month and who were followed-up for at least six months from the start of treatment.
2. Children who were postured either intermittently or for less than one month, or in whom the degree of propping was less than that stated for Group 1.
3. Patients given no postural treatment and who were between 6 months and 2 years of age when seen.

As shown in Table 4 a flattened head was only

TABLE 3
PROGRESS OF NINE PATIENTS BETWEEN 6 AND 24 MONTHS WHEN STARTED ON POSTURAL THERAPY

Case No.	Age of Starting Postural Treatment (months)	Supple- mentary Treatment	Clinical Progress			Age at Last Review		Remarks
			Severity of Symptoms and Age			Yrs	Mths	
			Frequent	Moderate	Minimal			
55	20	—	B-20 m 2 y 10 m- 3 y 6 m	20 m-22 m 3 y 6 m- 6 y 11 m	22 m- 2 y 10 m 6 y 11 m- LR	8	4	Postural treatment discontinued 2½ yrs; recommenced 3 yrs 4 mths (two pillows) until 6 yrs
62	17	Alkali, atropine	B-12 m	12 m-17 m	17 m-LR	4	0	Propping discontinued 2½ yrs
79	8½	Alkali	B-8½ m	8½ m-18 m	18 m-LR	7	6	Propping discontinued 3½ yrs
86	18	Alkali	9 m-18 m	18 m-20 m	20 m-LR	4	1	Propping discontinued 2½ yrs
101	18	—	B-LR	—	—	4	9	Propped 18 mths-2½ yrs; oesophageal stricture 2 yrs; repair of 'hiatus hernia' at 4 yrs 7 mths; good immediate symptomatic response
110	6	Alkali, atropine	B-18 m	18 m-2 y 4 m	2 y 4 m-LR	4	3	Propping discontinued 2 yrs
119	10	—	B-LR	—	—	5	3	Propping discontinued 2 yrs; oesophageal stricture 2½ mths
129	8	Alkali	B-18 m 18½ m- 3 y 6 m	18 m-18½ m —	3 y 6 m-LR	4	1	Treated by posture for 10 mths Oesophageal stricture 16 mths; repair of 'hiatus hernia' 18 mths; no improvement; resection of stricture and oesophago-gastrostomy 3½ yrs; improved; died 4 yrs 1 mth from neuroblastoma
160	14	—	B-18 m	18 m-2 y	2 y-LR	4	4	Postured for 12 mths

Abbreviations as in Table 1.

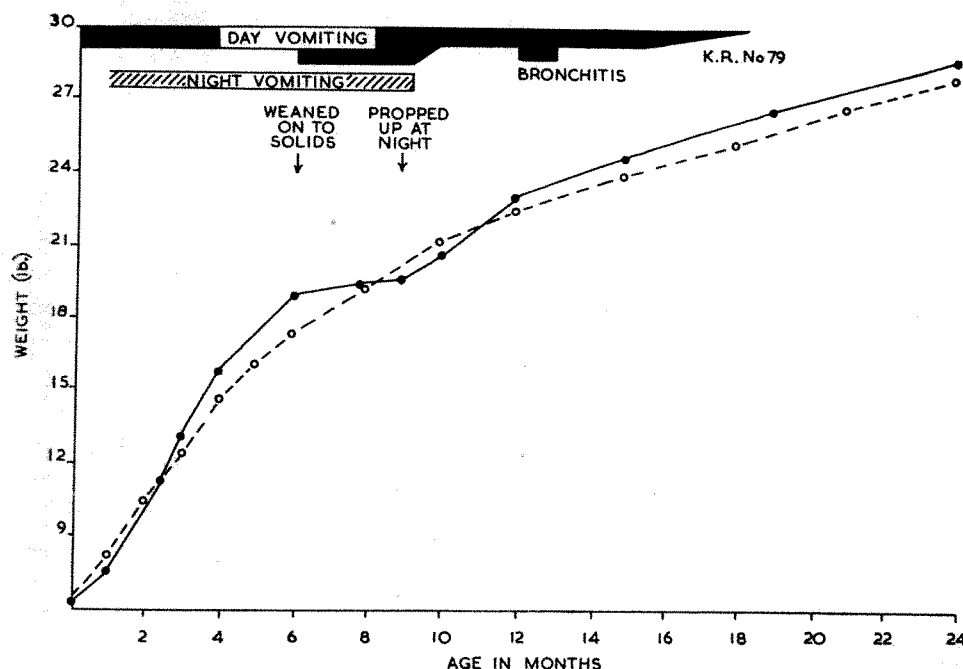


FIG. 3.—Despite vomiting from birth this infant gained weight satisfactorily until 6 months. During the following three months vomiting increased and no weight gain was recorded. No solid food was retained. From the time of starting postural treatment at 8½ months, vomiting at night, which had been a notable feature, ceased and dysphagia and day vomiting gradually subsided over a period of nine months. Except for an occasional vomit associated with respiratory infections this child remained free of symptoms up to his last review at 7½ years.

noted among children of Group 1; all were less than 3 months old when started on treatment. Eight of the 13 children who developed a 'flat' head were girls. Birth weights ranged from 4 lb. 14 oz. to 9 lb. 4 oz. with an average of 6 lb. 15 oz. Two children were noted as having developed a 'flat' head within one month of starting treatment.

Discussion

Value and Limitations of Postural Therapy. Postural treatment for the purpose of this review has been regarded as 'adequate' only if it entailed

TABLE 4
RELATIONSHIP OF POSTURAL TREATMENT TO
ALTERATIONS IN SHAPE OF HEAD

Age on Starting Postural Treatment (months)	Number of Patients		
	Group 1	Group 2	Group 3
0-1	31 (7)	6 (0)	11 (0)
1-2	11 (3)	6 (0)	
2-3	7 (2)	3 (0)	
>3	22 (0)	12 (0)	

Figures in brackets indicate number of patients with a 'flat' head.
For definition of groups 1, 2 and 3, see text.

keeping infants propped at 60° or more throughout the 24 hours. These requirements were originally formulated largely on the basis of theoretical reasoning during the early stages of this study in 1951.

By 1950 the aetiological importance of gastro-oesophageal reflux in the development of oesophagitis, ulceration and ultimately stricture formation in adult patients had been established (Tileston, 1906; Winkelstein, 1935; Dick and Hurst, 1942; Johnstone, 1943; Allison, Johnstone and Royce, 1943). Similar oesophageal changes noted in some children with a partial thoracic stomach appeared to have an identical aetiology as free gastro-oesophageal reflux was a frequently associated radiological feature. The damaging effect of gastric juice, hydrochloric acid and pepsin on the oesophageal mucosa had been demonstrated experimentally by Friedenwald, Feldman and Zinn (1928), Selye (1938) and Ferguson, Sanchez-Palomera, Sako, Clatworthy, Toon and Wangenstein (1950). There was, therefore, good evidence for supposing that the greatest danger to patients with gastro-oesophageal incompetence lay in the regurgitation of unbuffered and undiluted gastric juice.

Lelong, Aimé, Aubin and Bernard (1939) reported that infants with a 'brachyoesophage' were improved if nursed propped up after feeds. These observations were later confirmed by Wyllie and Field (1946), Nicod (1948) and Roviralta (1949). It seemed logical to postulate that the assumption of an erect posture by invoking the aid of gravity lessened the amount of gastro-oesophageal reflux in these infants which secondarily resulted in an amelioration of symptoms. On the basis of this reasoning it seemed particularly important that any such posturing should not be confined to short periods during the day or after feeds, but should be maintained throughout the night when the protective effect of food in buffering and diluting gastric contents was non-operative. Continued posturing throughout the 24 hours was therefore adopted as an essential requisite of 'adequate' therapy.

In addition to keeping patients propped up throughout the 24 hours, it soon became apparent that to be therapeutically effective posturing had to be of such a degree that patients were maintained in a sitting position (Fig. 1). It was found impossible to maintain this degree of propping without the use of some form of supportive harness or chair and for this reason postural treatment which did not include the use of some such appliance has been regarded as 'inadequate.'

No evidence has been obtained from this study favouring a relaxation of these measures. On the contrary, the results achieved have demonstrated that prolonged sustained propping in a sitting posture is essential if maximum benefit is to be obtained from this form of therapy. Whereas encouraging long-term results were recorded in the group of infants started on 'adequate' treatment by 3 months of age, a second comparable group given 'inadequate' therapy compared unfavourably. In fact, the ultimate prognosis of these latter children did not appear to have been materially influenced by therapy. These results also emphasize the importance of out-patient supervision. There is little doubt that an important factor contributing to the adequacy of treatment in the former group was the fact that patients were kept under regular out-patient observation. Though difficult of accurate evaluation, two features appeared to affect adversely the long-term response to treatment, namely maternal inadequacy, often aggravated by poor social conditions, and recurrent upper respiratory tract infections causing temporary exacerbations of vomiting.

It is possible to define two distinct clinical groups among infant patients based on their response to postural therapy. Of patients started on 'adequate'

sustained postural treatment by 3 months of age approximately two-thirds had virtually ceased vomiting within three months of starting treatment. By contrast, improvement in the remaining one-third was slow with troublesome symptoms persisting for many months. The relative proportions of these two groups, namely two-thirds and one-third, are identical to those of the two clinical categories recognizable among untreated infant patients, i.e. Groups I and II of the natural history study (Carré, 1959). This similarity in distribution suggests that the patients who responded promptly to treatment were in fact precisely those who, if untreated, would have undergone a spontaneous clinical cure by 2 years of age (Group I). Whereas, those whose improvement was slow and protracted were probably patients who, in the absence of treatment, would have suffered from troublesome symptoms to 4 years and older, with a few developing an oesophageal stricture as a complication (Groups IIa and b). Yet, with prolonged postural therapy eight of the 10 latter patients became virtually symptom free by 2 years of age; vomiting in four of these did not cease until after nine months of continuous therapy. The absence of a rapid symptomatic response should not be interpreted therefore as an indication *per se* for abandoning postural treatment.

Postural treatment when first started in late infancy or early childhood was not accompanied by such encouraging results as noted when treatment was started during the first months of life. Nevertheless, it seems that about half of the older patients are likely to benefit from postural treatment. There are two probable reasons why treatment should be less effective when first instituted at this age. The pathological changes in the lower oesophagus are more likely to be irreversible and, secondly, sustained adequate posturing is more difficult to achieve because of these patients' greater activity and strength.

Having regard to the recorded results and analytical precautions adopted, it is concluded that postural treatment is of considerable value in the management of infants with a partial thoracic stomach uncomplicated by an oesophageal stricture. To be maximally effective, however, treatment must be commenced as early in infancy as possible, and patients should be propped at 60° or more throughout the 24 hours. Treatment should be continued for as long as 12 months should troublesome symptoms persist; in refractory cases little additional benefit is likely to result from more prolonged treatment. In those patients who respond it is advisable to continue with treatment for a further

six weeks after the virtual cessation of all symptoms.

It must be appreciated that the effectiveness of postural treatment in this study has been determined solely by reference to clinical disturbances. Although of undoubted clinical benefit, there is no evidence that postural treatment influences the radiological 'cure' rate (Carré and Astley, 1960).

Postural treatment can only be regarded as routinely applicable if at the same time it can be asserted that no permanent undesirable ill effects are likely to accrue. Craig (1953) has recorded a flattening of the head in two infants with a 'hiatus hernia' treated by posture—an observation subsequently confirmed by Davies (1953). Thirteen similar instances have been noted among 98 patients treated by posture. All 13 children who developed a 'flat' head had been started on treatment before the age of 3 months and had been maintained continuously in a sitting posture for at least one month. These latter patients represented about one-quarter of the children so treated (Table 4). Not a single instance was seen among children treated by intermittent or lesser degrees of propping, among children over 3 months of age when started on treatment nor among untreated patients. The relationship of a 'flat' head to postural therapy is further emphasized by the findings in two sets of identical twins. One set was started on 'adequate' postural treatment at 10 days of age; both infants developed a 'flat' head. Of the other set of twins one infant was treated by posture from 7 weeks; the other received no postural treatment. The twin treated by posture developed a 'flat' head, whereas the other did not.

It might be thought that the skull of a premature baby would be softer and more malleable than that of a full-term infant and that as a result premature babies would be particularly liable to develop alterations in head shape. However, it was not possible to demonstrate any relationship between birth weight and the development of a 'flat' head in this series.

It is apparent that the 'flat' head seen in certain children with a partial thoracic stomach arises secondarily to the maintenance of an erect posture during the early months of infancy. That this abnormality may develop relatively quickly is illustrated by the two patients in this series who had developed a 'flat' head within one month of starting treatment. As these 'flat' headed children grow older the alteration in head shape becomes progressively less noticeable and it is probable, though not certain, that the abnormality eventually resolves completely.

That the propping up of small babies might result in eventual maldevelopment of the spine is often of justifiable concern to parents, and Braid (1953) has questioned whether prolonged treatment in an erect position might not interfere with normal pelvic growth. Though specifically looked for, no evidence of either spinal or pelvic maldevelopment has been noted among children in this series.

The introduction of thickened feeds was of great supplementary value in the few infants slow to respond to posture alone. Alkali and atropine derivatives were given so infrequently and sporadically that no reliable assessment of their therapeutic value is possible on the basis of this study. That these agents may have contributed to the symptomatic recovery of the few patients given these medicaments cannot be discounted. It may possibly be of significance that three of the four children whose treatment first started between 6 and 24 months of age and who either developed an oesophageal stricture or were still troubled with vomiting at 4 years of age had not been given alkali. On the other hand, of the five comparable patients whose symptoms at 4 years were 'minimal', four had been given alkali as supplementary treatment. In any case, until such time as unequivocal evidence to the contrary has been produced there seems to be, on at least theoretical reasoning, sufficient justification for the use of alkali as supplementary therapy.

Comparison of Published Results. Although only sufficient experience has been gained from this study to justify conclusions on the value and limitations of postural therapy, the published results of both medical and surgical treatment are briefly reviewed for the purpose of comparison. Only information relating to the treatment of children with a proven partial thoracic stomach uncomplicated by an oesophageal stricture is considered. Unfortunately, a strict comparison of published results with those of this study is largely impossible because of the frequent omission of essential data on methods and duration of treatment, length of follow-up, criteria of assessment and even more important the age and type of child treated. Moreover, most reported series include both medically and surgically treated patients. This raises an additional difficulty as it is seldom clear why patients were chosen to receive either one or other form of therapy. Because of the inevitable selection involved the results quoted in such reports need to be evaluated with considerable caution.

Good clinical results following conservative postural treatment have been claimed by Lelong, Aimé and Aubin (1941), Roviralta (1952), Fox and

Hunter (1954), Swyer (1955) and Burke (1959). Unfortunately, the information provided is insufficient to permit of comparison with the observations of this study. A very limited comparison has been possible with the observations of Masse and Bader (1957). For the most part patients seen by these authors were first treated conservatively and only if the immediate response to treatment was poor were they then subjected to operation. Analysis of their results shows that of children with a gastro-oesophageal abnormality corresponding to the partial thoracic stomach of this study, 38 started on a similar medical regimen of treatment within the first three months of life; 22 (58%) responded sufficiently promptly for operative treatment to be withheld (Masse, 1959, personal communication). These observations agree with those of the present review in which it was noted that among 54 comparable patients 35% became virtually symptom-free within two weeks and 72% within three months of starting postural therapy.

In contrast, unsatisfactory results from medical treatment are quoted by Forshall (1955) and Thomsen (1955). A critical evaluation of the information provided by these authors suggests how such a contrary opinion to that of this study has come about.

On the basis of experience gained in treating nine patients by postural methods Forshall (1955) expresses disagreement with the suggestion that many ultimately do well with conservative therapy. Details of the postural methods and duration of treatment are not stated nor is the patient's age on starting treatment. However, it would appear that at least five of the nine children were over 2 years of age and two had an oesophageal stricture. As illustrated in this study such patients represent precisely those who would not be expected, and indeed do not, respond well to medical treatment. It is important that these limited observations should be viewed in their correct perspective. Referring as they do to a particular type of patient it is clear that they should not be interpreted as representative of the results of medical treatment as applied to all children with a partial thoracic stomach.

Analysis of Thomsen's (1955) data shows that 24 patients were treated by postural methods for varying periods. The use of a harness or chair is not mentioned and it is probable that the degree of propping was less than that used in the present study. Two patients died from causes unrelated to the gastro-oesophageal abnormality. Of the remaining 22 only 12 were considered to have made a satisfactory response to conservative treatment. Eleven were diagnosed before 3 months of age and,

although by no means certain, it is assumed that their treatment will have dated from the time of diagnosis. With postural treatment as defined and applied in the present study 10 or possibly all would have been expected to respond. In fact only six became symptom free; their ages at the time of their last review varied from 15 months to 4 years. The other five children were considered to have failed to respond to treatment and were subjected to operation. However, consideration of the histories of these five patients indicates that in three at least postural treatment was maintained for less than six weeks. Had treatment been continued longer it is likely that these patients would also have responded. For, of comparable patients studied in this review about one-quarter showed little improvement until after three months continuous propping. The remaining 11 conservatively treated children in Thomsen's series were over 3 months of age when started on treatment. Such a group will include a high proportion of relatively severely affected children only about one half of whom are likely to respond to conservative measures. In fact, six of the 11 improved and became symptom free. Thus, although at first sight the results quoted by this author appear less satisfactory closer scrutiny reveals no significant difference from those of the present study.

A similar divergence of opinion exists with regard to the value of surgical treatment. Forshall (1955) records in a short follow-up review that surgical repair of the 'hiatus hernia' resulted in relief of symptoms in 29 of 30 children so treated. These are excellent results, but before giving credit to the surgical procedures employed it would be of considerable moment to know the age of these children at operation and, in view of its undoubted beneficial effect, to know if postural treatment was used to any extent either before or after operation. In any case a final assessment must await a more prolonged follow-up because of the possibility of relapse months after apparent surgical cure. In view of the therapeutic policy advocated by this author of 'operation in all cases in which the cardia is above the diaphragm' it can be assumed that most patients would have been operated on shortly after establishing the diagnosis, in which case the majority are likely to have been small infants. Should this in fact be so then the symptomatic results achieved are not notably different from those obtained in this review. Unfortunately, Forshall's encouraging results are not confirmed by other workers. Husfeldt (1953), for example, refers to the results of surgical treatment as being 'far from satisfactory'. Excluding three patients with an

associated oesophageal stricture only 10 of 24 patients were regarded by this author as cured following a surgical repair of the 'hiatus hernia'. Allowing for differing techniques, why should this surgeon's experience differ from that of the previous author? One important factor would seem to be the type of patient treated. In Husfeldt's series about half were over 2 years of age and there is little doubt that many had irreversible pathological changes in the oesophagus. It is noteworthy that of comparable patients treated by posture in the present study about half were similarly benefited.

Relatively disappointing surgical results have also been published by Guichard, Verger and Humeau (1956), Battex and Genton (1957) and Robb (1957).

Doubt regarding the efficacy of surgical treatment is expressed by Burke (1959) in a follow-up report on the series of patients originally reported by Waterston (1954). Of 64 surgically treated patients only 12 responded immediately with cessation of vomiting. Of the others 'improvement had sometimes begun before surgery was undertaken, but more often it was not evident until months or even years afterwards'. It should be noted, however, that 25 children in this series had an oesophageal stricture at the time of operation.

One other report dealing with the surgical treatment is that of Duhamel (1957). Excluding patients with an oesophageal stricture, 24 of this surgeon's patients had a gastro-oesophageal abnormality corresponding to the partial thoracic stomach of this study. An excellent or satisfactory response to therapy was noted in 20; four showed no improvement. Some degree of comparison is possible with the experience recorded in the present study. It is probable that most of the patients operated on had had a trial period of medical treatment beforehand in view of the therapeutic policy adopted by this author's medical colleagues (Masse and Bader). On the evidence of the present review the nine infants who were less than 6 months old when operated on by Duhamel would probably have improved over a period of months had postural treatment been continued. In fact, following operation two of the nine responded promptly, six made a slow recovery with gradual cessation of vomiting and one was not improved. These surgical results are not therefore significantly dissimilar to what would probably have occurred had postural treatment been more prolonged. On the other hand, of 15 children operated on when over 6 months of age seven made a prompt recovery, five improved slowly and three showed little clinical change. Assuming that all had troublesome symptoms at the time of operation these results reflect an

improvement on those of the present study for of comparable patients only about half benefited from prolonged postural therapy.

Although considerable experience in treating children with a partial thoracic stomach has been gained during the past few years, there exists no unanimity of opinion on the relative value of therapeutic procedures. In a disorder such as the partial thoracic stomach where there is such a wide variation in the naturally occurring clinical progress of individual patients it is imperative that strict analytical precautions should be adopted when assessing the value of therapeutic measures. Failure to do this and a lack of appreciation of the natural history have been mainly responsible for the controversial views expressed. For this reason the present study is considered to have an important subsidiary value. It is suggested that similar analytical procedures might usefully be adopted by other workers when assessing the results of either conservative or surgical treatment. If this were done there seems good reason to expect that many of the divergent views at present expressed would soon be resolved.

Summary

In this study the value and limitations of postural treatment in the management of children with a partial thoracic stomach uncomplicated by an oesophageal stricture have been assessed. The clinical progress of treated patients has been compared with the expected outcome as determined from a previous study of the natural history. All patients considered were followed-up to at least 4 years of age.

It is concluded that postural treatment is of great value in the management of these patients. To obtain maximum benefit it is necessary, however, that patients be sat up at 60° or more throughout the 24 hours. This degree of propping can only be maintained by using some form of supportive harness or chair. Treatment should be continued for up to 12 months should troublesome symptoms persist.

The most favourable clinical results were recorded in patients aged less than 3 months when started on treatment; 30 of 34 so treated were virtually symptom free at 1 year of age. On the other hand, only about one half of the older patients improved.

As supplementary treatment, thickened feeds were found to be of unquestionable benefit. The value of alkali could not be accurately ascertained though the available evidence suggests that this therapy is also helpful.

The only significant complication of treatment was the development of a 'flat' head in a few patients.

This alteration in head shape was confined to children who were started on treatment when under 3 months of age and maintained continuously in a sitting posture for at least one month.

A review of the literature is included showing that although much data have been collected during the past few years there still exists no unanimity of opinion and much confusion of thought on the relative merits of different therapeutic procedures. It is submitted that a failure to employ strict analytical methods when assessing the value of therapy combined with a lack of appreciation of the natural history have been the factors mainly responsible for the controversial views expressed.

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'SWEAT TEST' RESULTS IN NORMAL PERSONS OF DIFFERENT AGES COMPARED WITH FAMILIES WITH FIBROCYSTIC DISEASE OF THE PANCREAS

BY

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Many workers have confirmed the original observation of Darling, Di Sant'Agnese, Perera and Andersen (1953) that sweat sodium and chloride levels in children with fibrocystic disease of the pancreas are three to four times higher than those found in normal children. The reason for this has not yet been defined, but the difference is so clear in children that the 'sweat test' has become one of considerable diagnostic value.

However, the normal variation of sweat sodium and chloride levels in adults and in persons of varying age from childhood into adolescence and adult life has not been so clearly defined. Despite the absence of sound data of this type there is an increasing volume of literature in which the authors interpret small variations in these levels as an indication of abnormality in the groups of persons concerned. For instance, Di Sant'Agnese, Darling, Perera and Shea (1953) and Smoller and Hsia (1959) state that a proportion of parents and siblings of children with fibrocystic disease of the pancreas have somewhat raised sodium and chloride levels and that this indicates their carrier or heterozygous state; Hsia, Driscoll, Greenberg, Lee and Lanoff (1958) state that patients with allergies, particularly asthma, show higher levels than other children; Wood, Fishman, Reemtsma, Barker and Di Sant'Agnese (1959) state that some adult patients with chronic chest disease such as chronic obstructive pulmonary emphysema show raised levels and should be considered 'formes frustes' of fibrocystic disease of the pancreas.

Earlier work (Anderson and Freeman, 1958), in which a small group of parents and siblings were compared each with a group of normal adults and children failed to show any difference between the sweat sodium and chloride levels in the corresponding groups, but it did indicate that the levels in adults tended to be higher than those in children. This work has been extended to include groups of greater numbers, primarily to delineate the sweat

sodium and chloride levels throughout life. These levels have then been compared at the corresponding ages with those obtained in larger groups of parents and siblings of patients with fibrocystic disease. The levels in children with chronic or recurrent chest disease, including asthma, have also been compared with those of children of similar ages free from chest illnesses.

Materials and Method

Method. Sweating was stimulated by an intradermal injection of mecholyl hydrochloride, as described in an earlier publication (Anderson and Freeman, 1958); 2 mg. mecholyl was injected intradermally on the forearm in adults and older children and a smaller dose in babies and young children. Sweat was collected for one hour.

Sodium was measured by flame photometry. This estimation can be accurately made in amounts of sweat as small as 50 mg., which was all that could be obtained from some very young infants. In the majority of instances at other ages, over 100 mg. was obtained. Chloride was determined by the method of Schales and Schales. Owing to the relative inaccuracy of titration when chloride levels are low and small amounts of sweat are collected, sodium levels are considered to be the most reliable. Therefore sodium figures only are presented in this paper. There would be no difference in the general pattern of results if chloride figures were also presented but for the sake of clarity and accuracy they are not detailed here.

In our previous publication the level of 70 mEq./l. was chosen as the upper limit of normal and the lower limit of the fibrocystic level, but greater experience has shown that the vast majority of non-fibrocystic children under 15 years give values below 60 mEq./l. sodium, whilst a small percentage of fibrocystic values lie between 60 and 70 mEq./l. Consequently a dividing level at 60 mEq./l. is now taken but all results between 60 and 70 mEq./l. are checked.

Clinical Material. The following seven groups were studied:

1. One hundred patients with fibrocystic disease of the pancreas; these were all patients cared for medically

TABLE 1
COMPARISON OF SWEAT SODIUM LEVELS IN CHILDREN WITH FIBROCYSTIC DISEASE OF PANCREAS
WITH THOSE OF THEIR SIBLINGS, CONTROL CHILDREN AND CHILDREN WITH CHEST DISORDERS

Group	No.	Sweat Sodium Levels (mEq./l.)								
		0-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	>90
'Fibrocystics' ..	100	0	2	0	0	3	7	11	16	61
Controls ..	100	28	27	25	11	6	3	0	0	0
Chronic chest disease	100	23	31	28	15	1	2	0	0	0
Siblings ..	61	8	28	34	12	15	3	0	0	0

Numbers represent % of each group.

by one of us (C.M.A.) during a three-year period. The diagnosis was confirmed by clinical history and examination, and by at least one other test, i.e. the demonstration of pancreatic achylia or deficiency, or of steatorrhoea by laboratory techniques.

2. One hundred children up to 15 years of age used as controls; some of these children showed no organic disease and were tested purely as controls. The others were referred for diagnosis and showed conditions such as coeliac disease, steatorrhoea or failure to thrive. No child with subacute, recurrent or chronic chest symptoms is included in this group. Stools were always examined for excess fat in those who had failed to thrive and all children with steatorrhoea were shown to have normal pancreatic enzymes.

3. One hundred children up to 15 years of age who showed symptoms of subacute, recurrent, or chronic chest disease, but no digestive upsets or clinical evidence of pancreatic deficiency; these children comprise, first, a group, of whom the majority were infants, who were referred for a diagnostic sweat test because they had recurrent attacks of pneumonia or bronchitis; second, a group of patients with proven suppurative bronchiectasis all treated for a number of years by Dr. Howard Williams of the Royal Children's Hospital Chest Clinic; and third, a smaller group of children with chronic asthma who were also patients of the chest clinic.

4. Sixty-one siblings of the patients with fibrocystic disease of the pancreas; these were all under 15 years of age, were healthy, had grown normally and were within normal limits when examined clinically but did not undergo any other test to exclude fibrocystic disease of the pancreas.

5. One hundred adults over 20 years of age with no known disease; these were personnel working in the hospital and relatives and friends of the Clinical Research Unit staff.

6. One hundred parents of the patients with fibrocystic disease of the pancreas; these were all over 20 years of age and did not complain of any persistent diarrhoea or chronic cough.

7. Forty-seven adolescents between 15 and 20 years with no known disease; these were young nurses, office workers, laboratory technicians and school children.

Results

All groups contained individuals of both sexes in roughly equal numbers, but no difference in

sodium or chloride levels was noted between the sexes, although men usually produced a larger volume of sweat than women. Results are given with no further reference to sex.

Among the 100 whose diagnosis was considered to be that of fibrocystic disease of the pancreas and who were all under 15 years of age when first tested, all but five showed levels of sodium and chloride above 60 mEq./litre by the method employed. Sodium results are included in Table 1 where the actual number of children showing various levels are indicated. The two children whose sodium levels are between 20 and 30 mEq./litre were tested twice with similar results. They show other characteristics of the disease, are sisters, have pancreatic achylia and persistent suppurative chest infection of the type so familiar in this disease. The three children with sodium levels between 50 and 60 mEq./litre all have chloride levels above 60 mEq./litre. These children were retested with similar findings in one and higher results in the other two. However, the results recorded are the first performed, as is so with all groups. It can be seen that 95% of sodium values are higher than 60 mEq./litre, 61% being higher than 90 mEq./litre. Table 1 compares these results with the sodium figures obtained from the three other groups of children.

Among the 100 children up to 15 years of age who did not suffer from any chronic chest infection, allergy or pancreatic achylia, 97% of the sweat sodium values are below 60 mEq./litre with 80% below 40 mEq./litre. Among the 100 children with subacute or chronic chest disorders, 98% of sweat sodium values are below 60 mEq./litre with 82% below 40 mEq./litre, a scatter almost identical to that of children without chest symptoms. Among the 61 siblings of the patients with fibrocystic disease 59 or 97% were below 60 mEq./litre, 43 or 70% being below 40 mEq./litre.

Fig. 1 illustrates the results from the three groups of non-fibrocystic children giving a scatter according to age. The overall uniformity of scatter can be seen but as age progresses a somewhat upward trend in

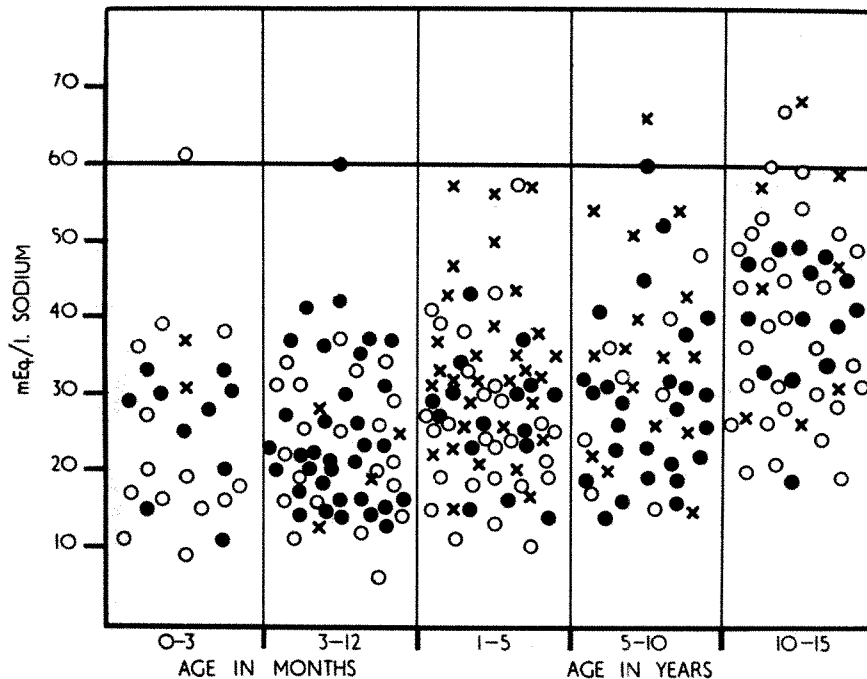


FIG. 1.—Sweat sodium levels in children of varying ages up to 15 years (the upper figure is included in each age group).
 ○ = normal children; ● = children with chronic chest diseases; x = siblings of children with fibrocystic disease of the pancreas.

values occurs in all groups. Combining the three groups it can be seen that up to 12 months of age all but four of the results are below 40 mEq./litre, but after that all age groups show more results between 40 and 60 mEq./litre and in the 10-15 age group about 50% of the values are at that level. Therefore up to the level of puberty the majority of values are below 40 mEq./litre, but there is a tendency for values to increase in later childhood.

There is no difference at all between the scatter of results for children with or without chest illness of non-fibrocystic origin. Among the siblings there are rather more children in the older age groups, for instance, 90% of them are over 12 months compared with 40% of the other two groups combined. Taking this into account there is no

significant difference between the results from the siblings and the other groups.

The results from the 100 normal adults (Table 2) and (Fig. 2) show a much wider scatter of results. A considerable number, 34%, were 60 mEq./litre and higher and only 23% were below 40 mEq./litre, a contrast to the non-fibrocystic children. The 100 parents of the fibrocystic children (Table 2 and Fig. 2) show a similar wide scatter of results with 39% over 60 mEq./litre and 19% below 40 mEq./litre. Although a few more results from parents are in the higher levels, notably the 70-80 mEq./litre group, there is a wide scatter of results and above 80 mEq./litre a very similar number to the normal adults. There is therefore no significant difference between the two groups of adults, although they

TABLE 2
 COMPARISON OF SWEAT SODIUM LEVELS IN 100 'NORMAL' ADULTS AND 100 PARENTS OF
 CHILDREN WITH FIBROCYSTIC DISEASE OF THE PANCREAS

Group	No.	Sweat Sodium Levels (mEq./l.)								
		0-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	>90
'Normal' adults	100	0	7	16	21	22	12	12	6	4
Parents of children with fibrocystic disease of the pancreas	100	2	3	14	15	27	14	16	6	3

Numbers represent % of each group.

differ significantly from the three groups of children up to 15 years.

The 47 normal adolescents between 15 and 20 years of age show results intermediate between those of the children and the adults with 11 or 24% above 60 mEq./litre and 13 or 27% below 40 mEq./litre (Table 3 and Fig. 2).

Fig. 2 gives the scatter of results of children, adolescents, adults and parents and indicates clearly the gradual increase in levels with age, the greater number of higher results after puberty as well as the wide variation of values in adult life. Table 3 combines all the non-fibrocytic results illustrating again the upward trend of values with increasing age, and shows the percentage of each group giving values below 40 mEq./litre, between 40 and 60 mEq./litre, and above 60 mEq./litre. From these

TABLE 3
COMPARISON OF SWEAT SODIUM LEVELS IN ALL GROUPS
STUDIED TO SHOW INCREASING VALUES
AT AND AFTER PUBERTY

Group	Sweat Sodium Levels (mEq./l.)		
	<40	40-60	>60
Control children	80	17	3
Children with chronic chest disease	82	16	2
Siblings of children with fibrocystic disease of the pancreas	70	27	3
'Normal' adolescents	27	49	24
'Normal' adults	23	43	34
Parents of children with fibrocystic disease of the pancreas	19	42	39

Numbers represent % in each group.

results it can be seen that about puberty and in adult life the level of 60 mEq./litre can no longer

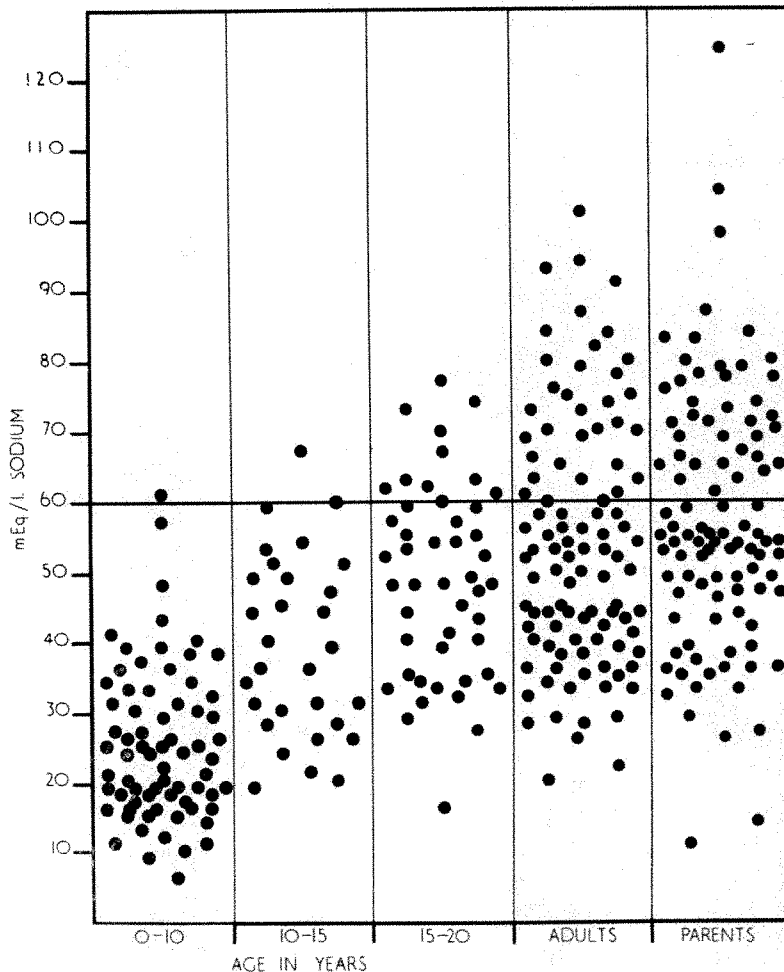


FIG. 2.—Comparison of sweat sodium levels in control children, adolescents, adults and parents of children with fibrocystic disease of the pancreas (the upper figure is included in each age group).

TABLE 4
INDIVIDUAL VARIATION IN SWEAT RATE AND COMPOSITION IN FOUR NORMAL ADULTS
WITH CONSTANT MECHOLYL STIMULUS

Date	Temperature and Climate	A		B		C		D	
		Sweat (g.)	Na Cl (mEq./l.)	Sweat (g.)	Na Cl (mEq./l.)	Sweat (g.)	Na Cl (mEq./l.)	Sweat (g.)	Na Cl (mEq./l.)
November 5, 1959	24° C.; slight humidity	0.1312	57 49	0.0611	56 79	0.3862	46 32	0.3249	77 58
November 26, 1959	28° C.; high humidity	0.1518	64 77	0.0959	67 68	0.3724	44 47	0.6606	62 49
December 12, 1959	24° C.; warm and dry	0.0944	45 47	0.0414	58 53	0.3283	46 31	0.3389	90 60
February 2, 1960	24° C.; warm and dry	0.1110	52 35	0.0688	79 58	0.3067	36 25	0.3395	60 41

A and B are female. C and D are male.

be considered as the dividing level between a normal and an abnormal level of sweat sodium.

Normal adults included individuals of varying ages up to the seventh decade and parents up to the fifth decade, but an analysis of these into age groups did not reveal any significant difference in levels. The increase in values was gradual in later childhood, becoming greater at puberty, but did not progress farther with old age.

Not only were the values from persons over the age of puberty likely to be higher, but results from individuals showed greater variation when repeated at intervals. To illustrate this variation four normal adults were tested at about monthly intervals and the results are recorded in Table 4. Here some indication is given of the climatic conditions of the day and amounts of sweat collected. Both sodium and chloride levels are indicated. This Table shows the considerable lability in sweat levels using as far as possible the same stimulus. No real correlation is seen with the climate, nor the volume of sweat and hence perhaps the rate, as the time of collection was constant.

Levels over 90 mEq./litre among the adults and parents were repeated if possible. There were seven individuals with values in this region. One male parent and one male adult were unavailable for retesting. Three of the other five showed lowered levels of retesting, although still above 60 mEq./litre. The remaining two, one female parent and one adult woman, showed consistent levels. The female parent, the only adult with a sodium level over 120 mEq./litre, was healthy but thin and had never had any chronic chest symptoms nor diarrhoea. A stool was normal in appearance and no fat globules were seen by microscopy. We believe this result to be a normal variant, but it is worthy of further investigation.

Chloride values are not recorded for reasons stated earlier, but the pattern of results in relation to age was very similar. 60 mEq./litre of chloride was still found to be the dividing line between 'fibrocystic' and 'non-fibrocystics' when considering children up to 15 years of age. In adults the sodium and chloride values did not approximate each other quite as closely as they did in children. Among the two groups of adults tested, i.e. 'normals' and 'parents', sodium figures were often slightly higher than chloride figures. However, this did not alter the comparison between the two groups of adults as there was still a comparable number of figures over 60 mEq./litre, for instance, 23% of normal adults and 25% of parents.

Discussion

Using a constant method of sweat stimulation and collection, levels of sweat sodium have been determined at various ages in childhood, adolescence and adult life. Fairly constant levels in infants and young children are found, but these levels rise slowly as age progresses and become very much more variable after puberty. Although the level of 60 mEq./litre of sodium can be said to be the upper limit of normal in the sweat of children under 15 years, such is not the case in adolescents and adults where many of the values are above this level. In all children under 15 who were tested, whether they are free from disease, suffer from chronic chest disease of non-fibrocystic origin, or are siblings of patients with fibrocystic disease, values are in the same range and 60 mEq./litre can be taken as the upper level. Taking into account the increasing values occurring after puberty there is also no difference in the pattern of results obtained from normal adults and from parents of patients with fibrocystic disease.

The two latter observations are at variance with those reported by some other workers, notably Di Sant'Agnese *et al.* (1953), Di Sant'Agnese (1957, 1959), and Smoller and Hsia (1959) who consider that levels of sodium and chloride in the sweat of some parents and siblings are higher than normal from which they deduce that these individuals are carriers of the abnormal gene of fibrocystic disease; and Hsia *et al.* (1958) who consider that children with chronic or allergic chest disease show higher levels than normal children. Our results, using a much wider range of controls, show no evidence to support these views. It is difficult to reconcile these varying results, but there are some factors which can be discussed.

A possible criticism of our results is that the method of obtaining sweat is not a satisfactory one. Among workers in the field of sweat electrolytes in fibrocystic disease of the pancreas a variety of methods have been used to stimulate sweating, but these fall broadly into two classes: sweating stimulated by heat or by other chemical agents. Results recorded by Di Sant'Agnese and his group and Hsia and co-workers are those of heat sweat. In the present study the method of sweat stimulation by intradermal mecholyl has been chosen for reasons outlined in a previous publication (Anderson and Freeman, 1958). As pointed out in that paper, the levels of sodium and chloride in sweat obtained in this way may be somewhat higher, occasionally up to 20 mEq./litre, than in sweat obtained by heat stimulation. However, this choice of method does not significantly affect the results obtained in the present study because all tests were done in the same way and can therefore be compared with each other, although not necessarily with those of other workers.

It might be possible that heat sweat produces a different pattern of values. However, study of the literature relating to normal sweating reveals a wide divergence in the range of results of sodium and chloride obtained by many workers. Notable amongst these references are the review by Robinson and Robinson (1954) and the monograph on 'Human Perspiration' by Kuno (1956). The former authors state that the concentration of sodium chloride in thermal sweat is extremely variable and give a list of 10 references in which values varying from as high as 100 to 148 mEq./litre down to 5 mEq./litre are reported, all on supposedly normal individuals and mostly adults. Kuno lists three groups of workers who find values as divergent as 400 to 17 mg. % sodium. They both point out the numerous factors such as skin temperature, climatic conditions, dietary intake of salt, and adrenal cortical activity, which can affect these levels and

Kuno in particular mentions age, discussing a control mechanism which begins to act on the sweat centres about puberty. Therefore it seems that our results in adults obtained by mecholyl stimulation parallel in the main those of many other workers, who were not concerned with fibrocystic disease of the pancreas.

Precise knowledge of the physiological control of the concentration of electrolytes in sweat has not yet been obtained, but many factors apparently affect these concentrations. The results presented here support Kuno's statement that age may be one of the factors and that about puberty there may be some physiological alteration in the control mechanism, or the factors that influence the concentrations may be playing a greater part, perhaps the endocrine factors. In view of the confusion that exists regarding the precise limits of normal variation of sweat sodium and chloride concentration in adults and the limitations of knowledge regarding the physiological control of these electrolyte levels, it is unwise to draw conclusions from the rather minor differences which some workers have observed in a proportion of parents and siblings of patients with fibrocystic disease and in some patients with chronic chest disease. In the work of both Di Sant'Agnese's group and Hsia and co-workers small groups of control adults are mentioned, but no attention paid to variation over a wide range of age.

A study of the literature devoted to the sweat sodium and chloride levels in patients with fibrocystic disease of the pancreas shows that differing levels are given by several authors as the upper limit of normal. The original contribution of Darling *et al.* (1953) stated that 60-70 mEq./litre of sweat sodium or chloride in heat sweat was the dividing line between normal and abnormal, but in a recent publication from the same centre (Di Sant'Agnese, 1959) the figure of 50 mEq./litre is given without adequate explanation of the change. Similarly, 50 mEq./litre is the upper level stated by Hsia *et al.* (1958) whilst 70 to 80 mEq./litre is the figure given by Shwachman and Leubner (1955). As there is still such variation among workers regarding the upper limit of normal for heat sweat it does not seem reasonable to theorize over levels between 50 and 70 mEq./litre obtained in parents and siblings (Smoller and Hsia, 1959), children with allergic chest conditions (Hsia *et al.*, 1958), or adults with chronic chest disease (Petersen, 1959).

The abnormal gene for fibrocystic disease of the pancreas appears to be a reasonably frequent one in the community and it might be argued that the adults and parents who showed values over 60 mEq./litre

in this paper were all heterozygotes. However, between 30 and 40% of both groups of adults tested came into this category and not even the most enthusiastic geneticist has yet placed the carrier rate at this level. The majority opinion suggests that the incidence of this disease in communities of Caucasian origin is in the region of one in 1,000 live births (Carter, in Bodian, 1953; Childs, 1956) and consequently, as the former writer states, the carrier rate would be about one in 15 or 6.5%.

If these higher results did indicate the carrier state then a proportion of siblings should show results in the same range, but in the data presented here they do not. Apart from the constant and clear difference between fibrocystic and non-fibrocystic children under 15 years of age there does not seem to be any other information relevant to fibrocystic disease of the pancreas than can at present be obtained from a study of the actual levels of sweat sodium and chloride, unless the reason for the varying and high levels found normally after puberty bears any relationship to the underlying defect in this disease.

As a consequence of the data presented here the determination of sweat sodium and chloride loses much of its value as a test for the diagnosis of fibrocystic disease of the pancreas in adults. We have already encountered difficulty in several adolescents and older persons who are suspected by certain clinical features of suffering from this disease. In these a very careful assessment of all features relevant to the disease should be made. As yet, there is insufficient evidence for the postulation of 'formes frustes' of the disease, but this will be discussed in more detail in a future publication.

The sweat abnormality or the abnormality of exocrine secretions in fibrocystic disease of the pancreas cannot yet be explained in basic terms, and until this can be done, slight abnormalities of sweat electrolytes should not be regarded as a genetic manifestation of the disease. Theorizing in this regard has preceded precise basic knowledge, and may give rise to misleading genetic counselling.

Summary

The range of sweat sodium and chloride levels obtained by stimulation with mecholyl in normal persons from birth to old age has been determined. A slight increase in concentration of these electrolytes has been found with increasing age in childhood. There is a greater increase and variation at and after puberty.

No difference has been observed in the results from

100 normal adults over 20 years of age and 100 parents of fibrocystic children.

No difference has been observed in the results from 61 healthy siblings of fibrocystic children and other children up to 15 years of age.

No difference has been observed in the results from 100 normal children and 100 children with chronic chest illness other than fibrocystic disease of the pancreas.

These results do not provide evidence that the carrier state in fibrocystic disease can be determined from raised levels of sweat sodium and chloride, nor that chest disorders in children show altered levels of these sweat electrolytes.

The 'sweat test' is of limited value in the diagnosis of fibrocystic disease of the pancreas in young adults or older persons.

Generalizations regarding genetic constitution in families of fibrocystic children should await further knowledge of the normal mechanism of control of sweat electrolytes and the basic defect in fibrocystic disease.

We should like to thank Miss R. Thomson for technical help with the electrolyte estimations, and Sister Pollock and her staff for help with the 'sweat tests', the many physicians of the Royal Children's Hospital who have referred patients to us, and the 'normal controls' who volunteered their help.

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THE SIGNIFICANCE OF INTIMAL THICKENING IN THE ARTERIES OF THE NEWBORN

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From both Europe and North America there have been a number of reports describing the presence of cushion-like areas of intimal thickening and elastic reduplication in the arteries of fetuses and infants (Dock, 1946; Fangman and Hellwig, 1947; Levene, 1956; Robertson, 1960a). The significance of these intimal cushions is uncertain. They are believed by some to be pathological in nature and the early lesions of atherosclerosis. Another view regards them as being a physiological adaptation of the vessel wall to mechanical stress and as having little influence in dictating the later development of atherosclerosis.

At Ibadan, coronary occlusion is rarely seen in the adult African and in the literature there are many reports indicating that atherosclerosis, certainly of the aorta and coronary arteries, is much less severe and extensive in the African Bantu and Negro than in Europeans (Davies, 1948; Edington, 1954; Hannah, 1958; and others). The present investigation sets out to determine whether intimal thickenings occur in the arteries of the African newborn and to compare their incidence with that found in European and North American subjects.

Methods

The popliteal artery of one leg was examined in 52 newborn African infants, 32 of whom were male and 20 female. Their ages ranged from fetuses of 30 weeks gestation to babies 2 weeks old. Most, however, were full-term stillbirths. In 30 of the cases, 19 male and 11 female, the proximal parts of the anterior descending and circumflex branches of the left coronary artery were also examined. From each vessel a small segment was taken and after fixation in formalin, paraffin sections were prepared and stained by haematoxylin and eosin and Weigert's elastic tissue stain counter-stained by van Gieson.

Findings

In the newborn the intima of the muscular

arteries consists of an elastic membrane, the internal elastic lamina, which is covered by the endothelium. The circular muscle of the media surrounds the intima and is bounded on its outer aspect by the adventitia. Of the 52 popliteal arteries examined, 42 (27 male and 15 female) showed areas in which there was a disturbance of this architecture. The pattern of this varied, but in most instances both the intima and media were affected to form a local cushion-like thickening of the wall. In the intima there occurred a reduplication of the internal elastic lamina so that several coarse lamellae or sometimes numerous fine elastic filaments were formed between which smooth muscle cells could be seen (Fig. 1). In the underlying media bundles of longitudinally orientated muscle also contributed to the thickening



FIG. 1.—Popliteal artery. Full term stillbirth. A cushion-like thickening of the wall is present over which there is reduplication of the internal elastica. (Weigert $\times$ 150.)

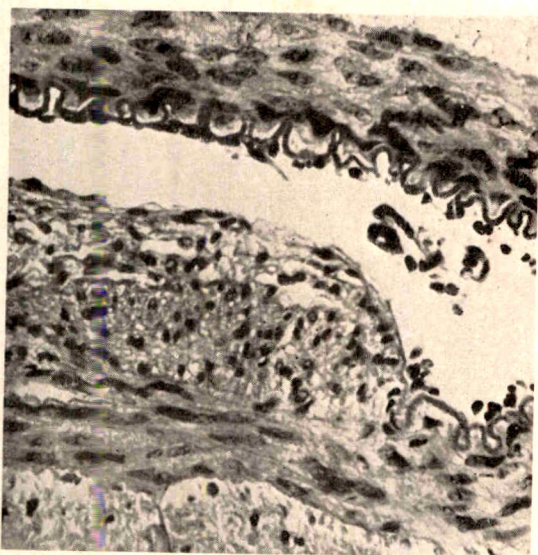


FIG. 2.—High power field of the cushion illustrated in Fig. 1. A band of longitudinal muscle is present in the media beneath the split elastica. (H. and E. $\times 300$.)



FIG. 3.—Popliteal artery. Full term stillbirth. A cushion showing marked reduplication of the internal elastica. The interstices of the elastic mesh contain many longitudinally orientated muscle cells. (Weigert $\times 86$.)

of the wall (Fig. 2). These longitudinal muscle bundles were the most conspicuous feature of many cushions and in some instances they formed the whole of the thickening, there being no reduplication of the internal elastica. Both the size and

complexity of the cushions varied widely, ranging from small nodes of longitudinal muscle in the media to the formation of large musculo-elastic mounds (Fig. 3). They occurred especially at the margins and opposite the mouths of branches, but were apparently not restricted to these sites, although serial sections would have been required to confirm this.

The left coronary artery was examined in 30 subjects and in 16 of these (11 male and five female) cushion-like thickenings of the wall similar to those of the popliteal artery were found. In the coronary vessels reduplication of the internal elastica tended to be more prominent than bundles of longitudinal medial muscle in the formation of the cushions. Only very occasionally, however, did a thickening show no evidence of a medial component. In both the coronary and popliteal vessels the van Gieson stain revealed strands of fibrous tissue in some of the cushions. It was generally associated with the elastic fibrils of the intima. In no instance was it present in large amount and many cushions showed no evidence of a fibrous component.

Discussion

Two views exist as to the significance of intimal thickenings in the vessels of the newborn. Fangman and Hellwig (1947) and Levene (1956) considered those in the coronary arteries to be pathological and the earliest lesions of atherosclerosis. Dock (1946) and Robertson (1960a) on the other hand, believed that they represented a response of the vessel wall to mechanical stress. In the coronary vessels Dock attributed this stress to the changing length to which these vessels had to adapt themselves during cardiac systole. Robertson, however, described similar thickenings in the popliteal and brachial arteries of the foetus and considered that their function was to buffer a stress due to tugging at the margins of branches and other points of fixation of the vessel during its elongation with pulsation. It was believed that the presence of intimal cushions was of no significance in determining the later development of atherosclerosis, although, if the disease did occur, it tended to localize in these regions of stress (Robertson, 1960b).

In the present study of newborn African subjects, cushion-like thickenings were found in the popliteal and coronary arteries of 81 and 53% of cases respectively. In both vessels the incidence was slightly higher in males than females. From these findings it appears that intimal thickenings occur just as frequently in the newborn of the African Negro as in those of the white races. Thus,

in a series of European fetuses, exactly similar structural changes were found in the popliteal artery of 76% of subjects (Robertson, 1960a) while, in North America, Fangman and Hellwig found coronary thickenings in 12 (40%) of 30 newborn infants, the incidence being higher in males than females. Despite the similar findings in the newborn of both races, most authors are agreed that atherosclerosis is less marked in the African Bantu and Negro than in Europeans. Higginson and Pepler (1954), for example, have found that only 3% of African compared with 32% of Danish subjects of the fourth decade have severe coronary and aortic lesions. The results of the present study therefore support the view that the presence of intimal cushions in the vessels of the newborn plays little part in determining the later development of atherosclerosis.

Summary

The presence of areas of intimal thickening and elastic reduplication in the popliteal and coronary arteries of newborn African infants is described.

Their incidence was found to be similar to that in the newborn of European and North American subjects. The significance of these thickenings in the pathogenesis of atherosclerosis is briefly discussed.

I wish to thank Professor G. M. Edington for his advice and encouragement during the course of this work.

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HISTIOCYTIC MEDULLARY RETICULOSIS IN A CHILD

BY

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Scott and Robb-Smith (1939), using the name 'histiocytic medullary reticulosis', reported four cases of a subacute illness characterized by fever, anaemia, leucopenia, jaundice and enlargement of the lymph nodes, spleen and liver. Microscopically there was a proliferation of phagocytes and giant cells in the reticulo-endothelial system, the affected tissues showing a tendency to undergo haemorrhage and necrosis. Marshall (1956a, b) described eight cases and referred to seven others reported in the literature since 1939.

The disease has not been reported in children and it is for this reason that the following case is mainly of interest. (For a review of the literature and discussion of various aspects of the disease Marshall's publications, 1956a, 1956b, should be consulted.)

Case Report

The patient was admitted to the Adelaide Children's Hospital on October 9, 1954, at the age of 4 years 5 months with generalized enlargement of the lymph nodes.

Her previous health had been good, apart from chickenpox and tonsillectomy, until three months before admission when a small lump in the right side of the neck had been noticed by her parents. A month before admission, because of a sudden increase in size of her neck, she was taken to a general practitioner who found rubbery enlargement of five or six lymph nodes in the right side of the neck. He could not feel the spleen at this time. Following treatment with antibiotics the nodes subsided considerably. Two days before admission they enlarged again, accompanied by a fever with a temperature of 102° F., tiredness and loss of appetite.

On admission to hospital the cervical, axillary and inguinal glands were all enlarged and the spleen was felt 3 fingers breadth below the costal margin. The liver could not be felt. Blood examination showed Hb 10 g./100 ml., the red blood cells numbered 3,800,000 per c.mm. and the white cells 8,800 per c.mm., 61% being neutrophils, 37% lymphocytes and 2% large lymphocytes. No abnormality was seen in a radiograph of the chest. A week after admission the Paul-Bunnell test gave agglutination at a serum dilution of 1 in 32, rising

to 1 in 64 three days later. Another blood examination on the day she left hospital, 11 days after her admission, showed Hb 12 g./100 ml., a white cell count of 14,800 per c.mm. of which 45% were neutrophils, 35% lymphocytes, 18% monocytes and 2% abnormal lymphocytes. Apart from two short bursts of fever, up to 100° F., her temperature was normal during her stay. On discharge from hospital her spleen could just be felt at the costal margin and the lymph nodes were much smaller. She was sent home to rest in bed, diagnosed as suffering from infectious mononucleosis.

On November 11, 1954, she returned to hospital with enlargement of the cervical lymph nodes which had apparently occurred over a few hours. Some fever had been noted five days before.

On examination she was pale and had very large fleshy lymph nodes in the right cervical region extending from behind the ear to the supraclavicular fossa. There was also enlargement of the nodes in the right axilla. The left cervical nodes were only slightly enlarged and no enlargement was felt in the inguinal regions. The spleen was enlarged to the level of the umbilicus but the liver could not be felt. The throat and middle ears were not inflamed.

Blood examination soon after admission showed Hb 10 g./100 ml. and a white cell count of 8,200 per c.mm.; bone marrow smears were normal. Further blood examinations during her illness showed a progressive fall in red and white cells and a later fall in platelets; Fig. 1 shows some of these changes. Reticulocytes never made up more than 2% except on one occasion when they reached 4% of the total red cell count. Four days after admission the lymph nodes were smaller but one from the right side of the neck was removed. Microscopical examination revealed that the general architecture of the node had been destroyed apart from some remaining cortical lymphoid follicles. In one part of the cortex was a wedge-shaped area of fibrosis containing scattered plasma cells. Elsewhere there was a mixed population of lymphocytes and plasma cells in an inconspicuous mesh of reticular cells, amongst which were scattered large, sometimes binucleated, mirror-imaged 'reticulum' cells. Reticulin fibrils were increased.

Fever began on November 22, the temperature remaining between 100° and 104° F., with rare falls to normal, until her death. No infective cause for this was found.

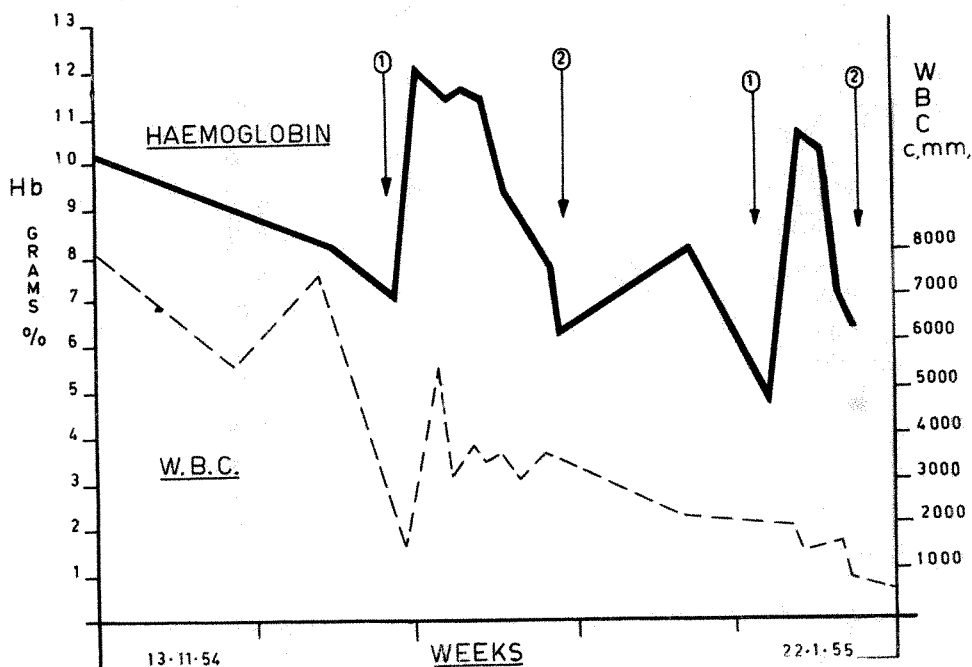


FIG. 1.—Haemoglobin and white count during final hospitalization. The numbered arrows indicate pints of transfused blood.

Blood cultures were negative and her serum did not agglutinate suspensions of *Salmonella* or *Brucella* organisms. In spite of the fever the lymph nodes and spleen began to subside on December 2, the spleen being just palpable by December 9, and the lymph nodes very small. A further aspirate of bone marrow on December 13, contained 27% monocyte-like forms, 13% lymphocytes, 41% polymorphonuclear white cells (with no excess of blast forms), 18% normoblasts and 1% plasma cells. Many of the monocytic forms had ingested red blood corpuscles, normoblasts, neutrophils and platelets (Fig. 2). A platelet count at this time was 120,000 per c.mm. A mild jaundice was noticed on December 22, and this increased steadily. By January 10, 1955, she was extremely wasted and deeply jaundiced; the lymph nodes had again enlarged to the size of marbles and the spleen and liver were easily felt. On January 13, a month since the last platelet count, the number had fallen to 14,000 per c.mm. and did not rise above this level again. At this time purpura and bruising appeared, followed by epistaxes and bleeding from injection sites. A direct Coombs test and a test of red cell fragility, both giving negative results, were not done until a few days before death, which occurred on January 21, 1955.

Findings at Necropsy. The autopsy (A.C.H. No. 8/55) was performed 60 hours after death. The body was extremely emaciated, deeply jaundiced, with numerous petechial haemorrhages in the skin. The pleural and abdominal cavities contained clear orange effusions. The enlargement of the lymph nodes involved all groups,

the cervical and axillary glands being most affected and the lower abdominal and inguinal nodes least. The cut surfaces of the glands were firm, pink to brownish purple with ill-defined yellow areas of necrosis. A few nodes were uniformly yellowish. The greatly enlarged spleen weighed 260 g., the serosal and cut surfaces showing irregular shaped yellowish areas up to 0.5 cm. in diameter, scattered over a dark purple background. The liver was enlarged and pale fawn, weighing 670 g. The sternal marrow was pale. The lateral muscles of the right thigh were soft and greyish, the overlying subcutaneous tissue haemorrhagic and the skin vesiculated, these changes being considered due to haemorrhage and infection at the site of injections. Both middle ears, but particularly the right, contained greenish pus from which a *Proteus* organism was isolated. Other organs showed no abnormalities apart from the effects of jaundice and anaemia.

Microscopically, identical changes were found in the lymph nodes and spleen. The architecture of the organs was largely replaced by a loose-textured moderately cellular tissue in which there was much haemorrhage and coagulation necrosis. The necrotic areas, particularly in the spleen, resembled small infarcts. The cellular areas consisted of a loose apparently syncytial proliferation of reticular cells, having oval vesicular nuclei and eosinophilic cytoplasm. Amongst this were typical macrophages which varied in number from place to place and many of which contained red cells and nuclear debris (Fig. 3). Another conspicuous but less numerous element was a giant cell having a large and

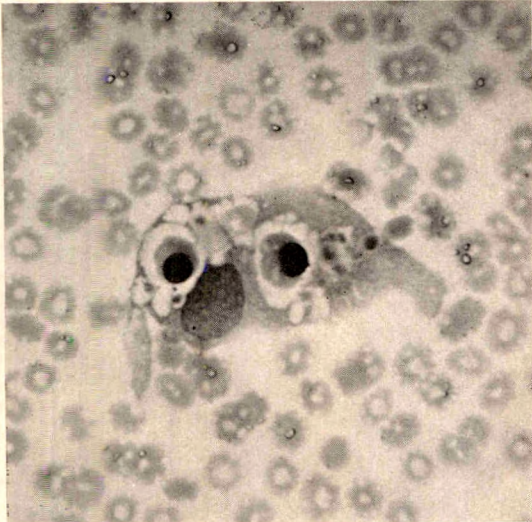


FIG. 2.—Bone marrow smear, showing a large phagocyte containing two red blood corpuscles, two normoblasts and platelets. (Giemsa $\times 750$.)

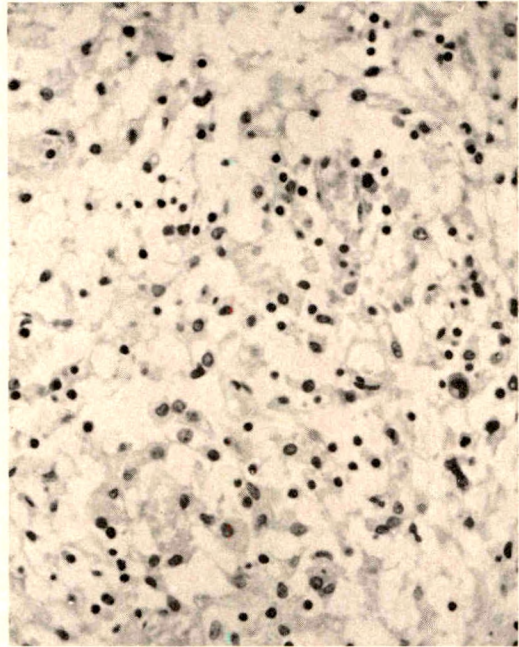


FIG. 3.—Lymph node, showing reticular arrangement of histiocytes. (H. and E. $\times 330$.)

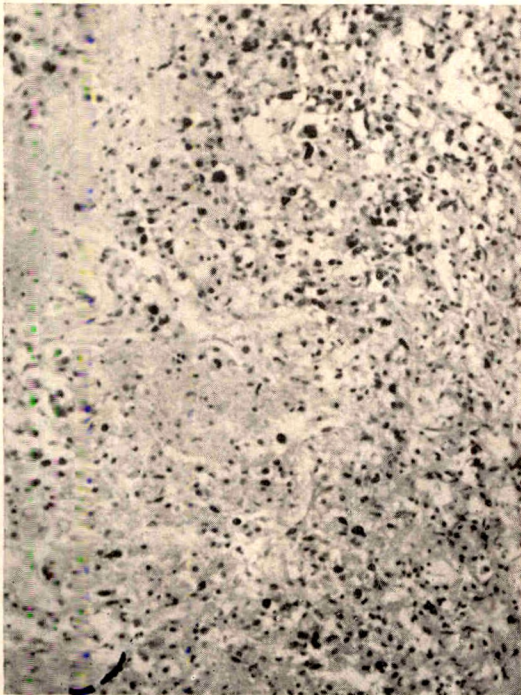


FIG. 4.—Lymph node, showing necrotic areas and densely staining giant cells. (H. and E. $\times 150$.)

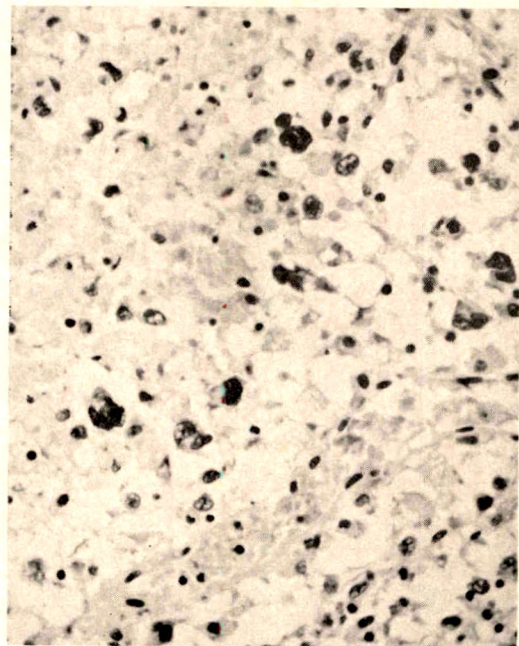


FIG. 5.—Lymph node, showing the irregular-shaped hyperchromatic nuclei of the giant cells. (H. and E. $\times 330$.)

hyperchromatic nucleus and a small amount of eosinophilic or occasionally basophilic cytoplasm (Fig. 4). The nucleus of the cell was commonly irregularly notched or folded, and if, as sometimes occurred, several nuclei were present these were closely packed together and unequal in size (Fig. 5). Transitions between these three main types of cell could be seen. Phagocytosis by the giant cells was not observed. Moderate numbers of mitotic figures were found, mostly in large cells. Mixed with this meshwork of histiocytic cells were small numbers of lymphocytes and many plasma cells and plasmablasts. A notable feature of the abnormal tissue was the large number of thin-walled blood vessels. In the lymph nodes the peripheral sinuses were usually preserved and contained many macrophages. In the spleen a few lymphoid follicles remained.

The sternal marrow showed almost complete replacement by tissue similar to that in the spleen and lymph nodes, except that giant cells were rare.

The liver had undergone a moderate degree of fatty change and congestion, and in addition contained occasional small haemorrhagic and necrotic foci of histiocytes and giant cells. Similar groups of tumour cells were found in the suprarenal cortex. Phagocytosis of red cells by Kupffer cells was present throughout the liver.

Other organs contained no significant changes. Perl's stain for iron revealed much haemosiderin in the spleen and Kupffer cells, but very little in the lymph nodes. Reticulin fibrils were increased in the lymph nodes.

Discussion

The clinical and pathological findings in this case conform in every way to the previous descriptions of the disease, except for the age of the patient. It is not proposed here to discuss the relation of this condition to other reticuloses; the pathological findings in the reticulo-endothelial organs are, however, quite singular. Nevertheless, the histological changes in the cervical lymph gland of the present case were considered by several pathologists to be typical of classical Hodgkin's disease, appearances which were to be completely replaced by the time of death two months later.

The relapsing nature of the illness also calls for attention, indicating that the course of the disease cannot be fully explained by neoplastic proliferation. The sudden enlargement of the spleen and lymph nodes may have been partly due to vascular engorgement rather than cellular proliferation alone. The equally sudden return of these organs to relatively normal size is hard to explain on other grounds.

The preliminary diagnosis of infectious mononucleosis could not be maintained, particularly as the Paul-Bunnell tests were performed with non-absorbed sera.

The rapid fall of the haemoglobin level following transfusions (see Fig. 1) suggested that the anaemia was due not solely to replacement of the bone marrow and this was confirmed pathologically by the discovery of widespread erythrophagocytosis and haemorrhage.

Summary

A girl of 4½ years presented with enlargement of the cervical lymph nodes and spleen, followed by anaemia, leucopenia, fever and enlargement of the liver. Jaundice, thrombocytopenia and a bleeding tendency appeared terminally.

A lymph node removed during life showed appearances typical of Hodgkin's disease but at death the reticulo-endothelial system was replaced by a proliferation of phagocytic histiocytes and giant cells.

I am grateful to Dr. Malcolm Cockburn for the use of the case record and to the Board of the Adelaide Children's Hospital for permission to publish the material. Thanks are due to Mr. Ray Boyd for the preparation of the illustrations.

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DEFICIENCY OF VITAMIN B₁₂ AFTER EXTENSIVE RESECTION OF THE DISTAL SMALL INTESTINE IN AN INFANT

BY

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(RECEIVED FOR PUBLICATION MARCH 2, 1960)

Man may survive resection of surprisingly large amounts of the small intestine. As little as 7 in. of jejunum and ileum may be sufficient to support life, at least for a time (Jackson, Linder and Berman, 1951), and a large number of patients have survived less extensive resections and have remained well (Flint, 1912; Heymond, 1935; West, Montague and Judy, 1938; Athausen, Uyeyama and Simpson, 1949). These observations have been made in adults and the results of extensive resections in children during the growing period are less certain. Such operations are infrequently carried out and there is a high immediate postoperative mortality (Benson and Sharpe, 1950). Children may, however, survive resection of large amounts of the small intestine (Blayney 1901; Flint, 1912), and two infants have recently been recorded whose growth and development were normal after resection of all but 26 to 28 cm. of jejunum and ileum (Pilling and Cresson, 1957).

The purpose of this paper is to describe a child who had an extensive resection of the distal small intestine soon after birth. She later developed a mild megaloblastic anaemia associated with severe B₁₂ deficiency and required treatment with vitamin B₁₂. Her growth and development have been otherwise normal up to the age of 2½ years.

Materials and Methods

Haematological methods were those described by Dacie (1956); serum vitamin B₁₂ levels were measured by microbiological assay using the Z strain of *Euglena gracilis*, according to the method described by Hutner, Bach and Ross (1956); glucose tolerance tests were carried out as described by King and Wootton (1956).

Fat balance was carried out over a continuous nine-day period. The child was given a diet containing approximately 30 g. of fat daily. After a preliminary period of three days, the stools were collected over successive three-day periods and the fat content was

estimated by the method of Van de Kamer, Huinink and Weyers (1949).

Absorption of radioactive vitamin B₁₂ was measured by the modified faecal excretion technique described by Booth and Mollin (1956). The test dose of vitamin B₁₂ was 1 µg. and was given with 50 mg. of a potent intrinsic factor concentrate.

Case Report

V.R., a female infant, was born at term on March 31, 1957, after a normal pregnancy (birth weight 7 lb. 5 oz.). Soon afterwards she developed signs of intestinal obstruction and was admitted to West Herts Hospital under the care of Dr. M. E. Edmunds. Laparotomy was performed on the 20th day of life and revealed congenital malrotation of the gut with volvulus and extensive gangrene of the small intestine. Approximately four-fifths of the distal small intestine were thought to have been removed, end-to-side anastomosis being performed between the jejunal stump and the mid-transverse colon. The terminal ileum was closed just proximal to the ileocaecal valve. After an initial period of severe vomiting and diarrhoea, she recovered from the operation, breast feeding was established and she gained weight.

At the age of 3 months she attended The Hospital for Sick Children, Great Ormond Street. At this time she was passing two to five bulky fluid stools daily. She weighed 9 lb. 4 oz., and apart from some abdominal distension, no abnormality was found on examination. She continued with breast feeding and supplements of vitamins A, C and D by mouth. By the age of 6 months her weight (15 lb.) was above the 10th percentile level. Although she continued to have diarrhoea, her weight increased at a normal rate until she was 10 months old, when she weighed 19 lb. (Fig. 1). During the 11th month, however, there was a gradual diminution in the frequency of her stools; she began to vomit after her feeds and she lost weight. She was then admitted to The Hospital for Sick Children at the age of 11 months under the care of Dr. P. R. Evans.

Clinical Examination. This revealed a thin child (weight 16 lb. 10 oz.) with generalized abdominal

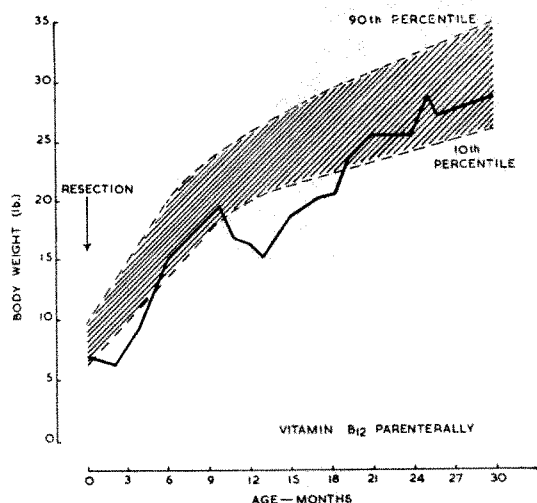


Fig. 1.—Weight chart of patient V.R. after extensive resection of the distal small intestine. Vitamin B₁₂ was given parenterally after the thirteenth month. The lines representing the 10th and 90th percentile are also shown (Tanner, 1958).

distension. No peristalsis was visible. There was no glossitis nor angular stomatitis. The skin was normal and the central nervous system showed no abnormalities.

Investigations. These revealed Hb 12.1 g. % and R.B.C. 4.0 M. per c.mm.; serum electrolytes: Na 140, K 4.2, Cl 102 and HCO₃ 26 mEq./litre. Stool cultures were repeatedly negative for pathogenic organisms. Plain radiographs of abdomen showed gross gaseous distension with fluid levels in both colon and small intestine.

Treatment and Progress. She was first given oral neomycin (20 mg./lb. body weight in divided doses), but without improvement in her condition. The vomiting, periods of constipation and the radiological evidence of fluid levels in the bowel suggested a diagnosis of subacute intestinal obstruction. A further laparotomy was therefore performed on March 19, 1958, but although the whole of the large bowel and the jejunum immediately proximal to the anastomosis appeared dilated, no organic obstruction was found. The remaining small intestine consisted of the duodenum and approximately 30 in. of jejunum, the end of the jejunum being anastomosed to the middle of the transverse colon, thereby short circuiting the caecum, ascending colon and proximal half of the transverse colon. Nothing further was done and the abdomen was closed.

Her condition continued to deteriorate after this operation. Her weight fell steadily (Fig. 1), vomiting continued intermittently and her stools were bulky and irregular. However, barium meal showed the small intestine to be normal, the barium passing into the colon in one and a half hours. A barium enema outlined the dilated colon but some of the barium remained for five

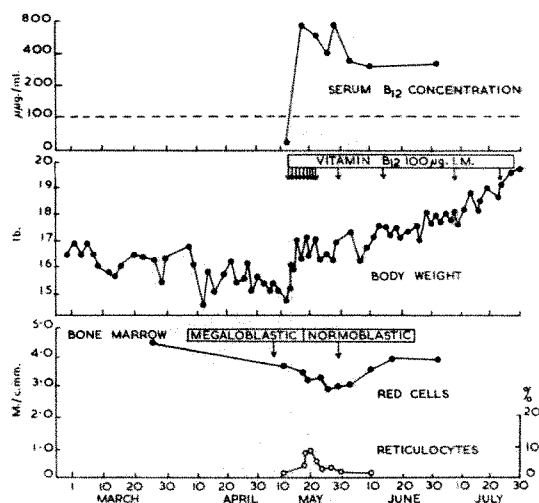


Fig. 2.—Serum B₁₂ concentration, body weight, red cells and reticulocytes before and after treatment with vitamin B₁₂.

days in the short-circuited ascending colon and caecum, indicating stasis in this loop.

By May 1958, at the age of 13 months, her weight had fallen to 15 lb. (Figs. 1 and 2). Haematological investigations now revealed a mild macrocytic anaemia (Hb 11.0 g. %; R.B.C. 3.7 M. per c.mm.) and the bone marrow was megaloblastic. Her serum B₁₂ concentration was 25 μg. per ml. (normal range 140 to 900 μg. per ml.). Intestinal function tests were carried out at this time and are shown in Fig. 3. Her absorption of glucose was normal but she had steatorrhoea (mean fat absorption 82% on diet of 30 g. per day) and she was unable to absorb any of the test dose of vitamin B₁₂ (Fig. 3).

Response to Vitamin B₁₂. She was treated with intramuscular injections of vitamin B₁₂ (100 μg. daily for nine days, then 100 μg. every two weeks). Her initial response to this treatment is shown in Fig. 2. Vomiting ceased within 24 hours of the first injection and her weight began to increase. Her reticulocytes rose to 9% on the sixth day and the marrow became normoblastic. Although her red cell count fell at first, possibly as a result of rehydration, it then rose to normal levels without other treatment (Fig. 2).

Further investigations revealed no evidence of other deficiencies. Her total serum proteins were 7.0 g. %, serum Ca 8.8 mg. %, inorganic phosphate 5.6 mg. %, and alkaline phosphatase 24 King-Armstrong units. Skeletal radiographs revealed no evidence of rickets. Prothrombin time was normal. Intestinal function studies were repeated after oral chlortetracycline (20 mg./lb. in divided doses for six days). There was no improvement in absorption of either fat or B₁₂ following this treatment (Fig. 3).

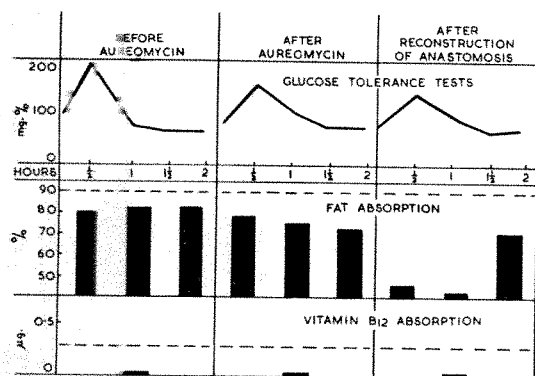


FIG. 3.—Intestinal function tests before and after chlortetracycline (aureomycin) and after refashioning of the jeuno-colic anastomosis. The figures for fat absorption represent the mean absorption per day over successive three-day periods. Normal fat absorption should be greater than 90%. The lower limit of the absorption of radioactive B₁₂ by control subjects is indicated by the interrupted line.

Her weight increased steadily, although her stools were unchanged, and she weighed 19 lb. after two months' treatment with vitamin B₁₂ (Fig. 2). A further laparotomy was performed on July 30, 1958 (Mr. G. H. Macnab). The jeuno-transverse anastomosis was undone, and an end-to-end anastomosis was made to the caecum. During this procedure many adhesions around the jejunum were broken down. The jejunum appeared slightly hypertrophied immediately proximal to the anastomosis but the remaining small bowel was of normal calibre. A biopsy taken from the lower end of the jejunum showed normal mucosa, but some hypertrophy of the muscle coats.

She recovered well from this procedure and continued to improve, although a fat balance revealed more marked steatorrhoea than before the operation (mean fat absorption 82% on diet of 30 g. per day). Her glucose absorption remained normal, but she was still unable to absorb vitamin B₁₂ (Fig. 3).

After this operation she received a diet usual for her age with restriction of fat to 30 g. per day, together with oral supplements of vitamins A (7,000 units daily), B (Becosym 1 dram daily) and D (1,000 units daily). She was also given vitamin B₁₂ intramuscularly (100 µg. every two weeks). Her subsequent progress is shown in Fig. 1. By 20 months her weight was above the 10th percentile and her development has continued normally. Now, at the age of 2½ years, she weighs 28·5 lb., a normal weight for her age. Her Hb is 10·9 g. % and she remains well, although she still passes three bulky stools daily.

Discussion

Estimations of the amount of small intestine remaining after resection are notoriously inaccurate (Flint, 1957). At our patient's first operation, it was considered that four-fifths of the small intestine had been removed. The remaining intestine was

measured at a later laparotomy and was found to consist of approximately 30 in. of jejunum. The exact length of the small intestine in an infant is not certain and the proportion of the bowel remaining in this patient is therefore not known, but in this case 30 in. may possibly represent between a quarter and a third of the total small intestine.

The type of malabsorption from which she suffered was characteristic of an extensive resection of the distal small intestine (Booth, 1958). Since some of her proximal intestine remained, she absorbed glucose normally, for glucose is rapidly absorbed from the upper small intestine (Verzár and MacDougall, 1936). Her remaining intestine was apparently only sufficient to absorb between 52 and 82% of her dietary fat and she therefore had steatorrhoea, suggesting that fat is normally absorbed more distally than glucose in the small intestine. Her inability to absorb vitamin B₁₂ is in keeping with the resection of the distal small intestine, for B₁₂ is absorbed in the ileum in man (Booth and Mollin, 1959).

Stagnant loops of bowel may sometimes play a part in causing malabsorption (Cameron, Watson and Witts, 1949; McIntyre, Sachs, Krevans and Conley, 1956; Halsted, Lewis and Gasster, 1956), but do not appear to have been a factor in this case. In patients with such loops, malabsorption is frequently improved by a course of oral broad spectrum antibiotics (Mollin and Baker, 1955; McIntyre *et al.*, 1956; Halsted *et al.*, 1956; Booth and Mollin, 1957) or by operations which remove or correct the loop (McIntyre *et al.*, 1956). Our patient's absorption defects were not improved by antibiotics, nor by the removal of the short circuit at her last operation, and it seems unlikely that the short-circuited area of colon contributed to her malabsorption. The reason for her deterioration in fat absorption after this operation is uncertain, but it may be that the breaking down of adhesions around the lower jejunum resulted in more rapid passage of food through the remaining small intestine.

For the first 10 months of life her growth was normal, suggesting that she was able to absorb or derive from tissue stores sufficient nutrients to maintain normal development during this time. Since she was unable to absorb vitamin B₁₂, it is not surprising that she ultimately developed B₁₂ deficiency. The delay in onset of this deficiency was presumably due to the time required to exhaust the stores of vitamin B₁₂ in liver and other tissues, a situation which is analogous to the delayed development of B₁₂ deficiency after total gastrectomy (Pitney and Beard, 1955). The symptoms and

signs in our patient were different from those usually found in adult patients with Addisonian pernicious anaemia. She had vomiting, constipation and signs suggestive of intestinal obstruction, and she lost weight steadily. There were no neurological signs suggesting subacute combined degeneration of the cord or peripheral neuritis. Despite her very low serum B_{12} level, she was not markedly anaemic, her red cells never falling below 3.0 M. per c.mm., although her sternal marrow was megaloblastic.

Her full and complete response to parenteral injections of vitamin B_{12} suggests that although she had marked steatorrhoea, the only deficiency state she had developed was B_{12} deficiency. This observation is supported by the absence of hypoproteinaemia, her normal prothrombin time and the lack of evidence of rickets. Since she has continued to grow normally whilst receiving only vitamin B_{12} parenterally, she appears to be absorbing the other nutrient factors required for growth and development. These factors, including the vitamins other than B_{12} , must therefore be absorbed in the proximal small intestine or colon.

It is not certain whether there is any compensatory improvement in intestinal function in children after extensive resections, although adults may show a progressive increase in absorptive capacity following such operations (Althausen, Doig, Uyeyama and Weiden, 1950). It is said that the mucosa and muscle of the remaining gut typically hypertrophies (Flint, 1912; Jackson, 1958), but this does not always occur (Shonyo and Jackson, 1950; Shelton and Blaine, 1954) and in animals the site of the resection may play a part in determining whether there is hypertrophy of the remaining small bowel (Booth, Evans, Menzies and Street, 1959). In our patient, the barium follow-through showed no evidence of hypertrophy of the small intestine, but at laparotomy the lower jejunum was found to be hypertrophied. It is uncertain whether this was due to partial obstruction by the many adhesions found in this area at her last operation, or whether there has been hypertrophy which was compensatory to the loss of intestinal length. It seems unlikely that she will recover the ability to absorb vitamin B_{12} and treatment with vitamin B_{12} by injection is to be continued indefinitely.

The observations in this patient illustrate the importance of the distal intestine in the absorption of vitamin B_{12} . They also support the conclusion that patients who have undergone resection of the ileum should either be kept under close haematological supervision or be treated with prophylactic injections of vitamin B_{12} .

Summary

Extensive resection of the distal small intestine was performed in a child soon after birth. Her growth was normal until she was 10 months old when she began to vomit and lose weight. At the age of 13 months she was found to have a mild megaloblastic anaemia and her serum B_{12} concentration was very low. She improved dramatically after treatment with parenteral B_{12} and her growth and development have been normal to the age of 2½ years.

We wish to thank Dr. P. R. Evans and Mr. G. H. Macnab for permission to record details of this patient who was under their care in The Hospital for Sick Children, Great Ormond Street; we are also indebted to Dr. D. L. Mollin for his encouragement and advice, and for permission to quote the results of vitamin B_{12} studies carried out in his laboratory at the Postgraduate Medical School.

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CHRONIC NON-HAEMOLYTIC JAUNDICE WITH CONJUGATED BILIRUBIN IN THE SERUM AND NORMAL LIVER HISTOLOGY: A CASE STUDY

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Recently our knowledge of bilirubin metabolism has increased considerably. Perhaps the most stimulating discovery has been that bilirubin is excreted in the bile as a glucuronide (Billing, Cole and Lathe, 1957; Schmid, 1957). This has made it possible to classify some rare types of chronic jaundice more definitely. One of these, chronic non-haemolytic familial jaundice, was described many years ago by Gilbert and Lereboullet (1901). Arias and London (1957) concluded from *in vitro* experiments with liver tissue that the cause of this disease was a defect in glucuronide formation. The inability to form glucuronides is also present in the much more severe type of inherited chronic jaundice with kernikterus described by Crigler and Najjar (1952) (cf. Axelrod, Schmid and Ham-maker, 1957).

Neonatal jaundice also belongs to this group, characterized by insufficiency of glucuronyl-transferase in the liver (Dutton, 1959), but, in contrast to the diseases mentioned above, is a passing phenomenon, present only in the newborn period (Vest, 1958; Vest and Streiff, 1959).

There is another group of chronic non-obstructive, non-haemolytic jaundice in which no such defect in glucuronide formation is present. In consequence a substantial percentage of 'direct' reacting bile pigment is found in the serum, and bilirubin spills over into the urine. This group includes the form named chronic idiopathic jaundice (Dubin and Johnson, 1954), which is conspicuous by the presence of a pigment similar to lipofuscin in the liver cells (cf. Dubin, 1958). Clinical symptoms are fluctuating jaundice, episodes of abdominal pain, nausea, vomiting, enlarged liver and dark urine. Bromsulphalein retention is greatly increased.

A few reports have appeared on a syndrome similar to the Dubin-Johnson syndrome, where the characteristic pigment was missing on examination of the liver tissue (Rotor, Manahan and Florentin,

1948; Schiff, Billing and Oikawa, 1959; Haverback and Wirtschafter, 1960). There are some other small differences in symptomatology from the Dubin-Johnson syndrome. Most important of these are the absence of attacks of abdominal pain and the fact that the gall bladder can be easily seen on oral cholecystography. Only six patients with this syndrome have been described in the literature so far, to our knowledge. This makes it difficult to decide if the observed differences are constant features of this disturbance of bile pigment metabolism or if they are a variation of the pigmented type of chronic idiopathic jaundice.

The patient described here seems to belong to the non-pigmented group and is presented in the hope of further clarifying the picture of this pigmentless type of chronic non-haemolytic jaundice without insufficiency of glucuronide formation.

Case Report

W.M., a 7-year-old girl, born in 1952, is the only child of a family from southern Switzerland. The family history gives no indication of liver or blood disease; the pregnancy was normal and the child's birth weight was 3,270 g. At the age of 4 weeks the mother observed a yellow tinge in the skin and this slightly icteric appearance has persisted. It is visible especially in the sclerae, but at times it increases in strength to an overt jaundice. When this happens the child is tired and anorectic, but there is no abdominal pain. Sometimes during these attacks the stools are paler than normal and the urine is dark. After a few days these symptoms subside. At the age of 13 months and 16 months the girl was seen by a paediatrician who found no abnormalities apart from icteric sclerae. Liver and spleen were not enlarged, Hb was 67% and 76% respectively. At the age of 28 months the patient was admitted to our hospital because of persistent jaundice.

First Admission. On admission skin and sclerae were icteric. The liver was palpable one finger-breadth below the costal margin; the spleen was not enlarged.

Haematological studies showed no abnormalities with the exception of a slightly higher proportion of smaller cells than normal in the Price-Jones curve. Several times the fragility to hypotonic saline solutions was a little increased, total haemolysis occurring at from 0.49 to 0.51%. These features were not persistent, however, and on other occasions normal values were observed. The direct Coombs test and indirect antiglobulin tests for antibodies were negative. Serum bilirubin level was high and varied between 7.2 and 4.2 mg. % with a moderate to strong direct van den Bergh reaction. Urobilinogen level in the urine was also high, but surprisingly no bilirubin could be detected in the urine with the method used at that time.

Extra-hepatic obstruction was thought unlikely from the benign course and from the normal aspect of the faeces. Also, on duodenal aspiration, normal enzyme activity (trypsin, diastase and lipase) was present in the duodenal secretion and A, B and C bile of normal appearance and in normal amounts could be aspirated. Other laboratory findings are shown in Table 1.

Because of the slightly increased red cell fragility and spherocytosis a mild form of hereditary spherocytic anaemia was assumed at that time, despite the rather high bilirubin concentration in the serum and the fact that no abnormalities were found in the parents.

Second Admission. In 1959, at the age of 7½ years, the patient was readmitted for further studies because of her persistent slight jaundice with occasional exacerbation. On admission the height was 120 cm. and body weight 23.7 kg. There was a reddening of the throat and a throat culture produced haemolytic streptococci. The antistreptolysin titre was 1:320. Otherwise physical examination was negative, except for the icteric sclerae. Liver and spleen could be felt at the costal margin.

TABLE 1
LABORATORY FINDINGS

Investigations	1955	1959
Haemoglobin ..	87%	90%
Red cells, millions/mm. ³ ..	4.36	4.26
Colour index ..	1.0	1.07
Anisocytosis ..	slight	slight
Leucocytes per mm. ³ ..	7,300	9,150
Neutrophils stab ..	7.5	15.5
Neutrophils segmented ..	22.5	55
Neutrophils eosinophil ..	—	0.5
Neutrophils basophil ..	—	—
Monocytes ..	12.0	5.0
Lymphocytes ..	58	23.5
Plasma cells ..	—	0.5
Reticulocytes % ..	3.5	1.3
Platelets ..	286,000	81,000-160,000
Haematocrit % ..	43	—
Ratio of red cells to white cells in bone marrow ..	26/100	12/100
Price-Jones curve ..	slight shift to left	normal
Osmotic fragility: beginning of haemolysis ..	0.45 to 0.53%	0.49%
total haemolysis ..	0.39 to 0.41%	0.35%
Direct Coombs test ..	negative	negative
Indirect antiglobulin test ..	negative	—
Auto-antibodies ..	negative	—
Wassermann reaction ..	negative	—
Prothrombin ..	80-100%	40-100%
Coagulation time ..	5 min.	3 min.
Bleeding time (sec.) ..	45	90

TABLE 2
LIVER FUNCTION TESTS

Investigations	1955	1960
Serum bilirubin (mg. %) ..	4.2-7.2	3.7-5.0
Direct ..	+	2.2-3.5
Cholesterol (mg. %) ..	—	177
Esters ..	—	72%
Total protein (g. %) ..	—	5.3-6.7
Serum iron (µg. %) ..	54-86	116
Blood sugar (mg. %) ..	93	—
Serum alkaline phosphatase ..	—	12
Takata-Ara ..	(+)	+
Cadmium reaction ..	—	trace
Thymol turbidity, units ..	—	2.3
Transaminase: SGOT, units ..	—	29
SGPT, units ..	—	12
Galactose tolerance ..	normal	normal
'Bromsulphalein' retention ..	—	51% and 48%
Hippuric acid test ..	—	low normal
NAPA-test for glucuronide formation ..	—	normal
Urine: Urobilinogen ..	increased	4.9 mg./24 hrs
Bilirubin ..	—	0.62 mg./24 hrs
Coproporphyrin ..	—	trace
Melanin ..	—	negative
Duodenal fluid: Trypsin ..	normal	normal
Diastase ..	normal	normal
Lipase ..	normal	normal

BLOOD FINDINGS. The red cell count was 4.26 million, Hb 89% and colour index 1.07. Some anisocytosis was discernible. Reticulocytes 1.3%; white cell count 9,150 per c.mm. The differential count and additional haematological data are listed in Table 1.

LIVER FUNCTION (Table 2). Takata-Ara reaction was one plus; cadmium, a trace; thymol-turbidity 2.3 units; total serum protein 5.35 and 6.7 g. %. Paper electrophoresis revealed albumin 48%, α₁-globulin 5.8%, α₂ 11.6%, β 13.4%, and γ-globulin 21.2%. The increase in γ-globulin was probably produced by the existing throat infection. Serum transaminase glutamic oxalacetic, 29 units; glutamic pyruvic, 12 units; serum alkaline phosphatase, 12 units; cholesterol, 177 mg. %; cholesterol esters, 72%. The prothrombin activity was 40% on admission, but afterwards, on repeated determinations, was always normal.

Serum bilirubin determination (methods of Jendrassik and Gróf, 1938; Malloy and Evelyn, 1937) gave values between 5.0 and 4.1 mg. % for total bilirubin, the direct reacting pigment being 3.5 to 2.2 mg. %. Paper chromatography of the serum by the method of Schmid (1957) showed two bands of azoderivatives with an R_f of 0.46 and 0.58.

URINE. Urines generally were rather dark in colour. Urobilinogen excretion (average of two 24-hour collections) amounted to 4.86 mg. per day and therefore was greatly increased (method of Schwartz, Sborov and Watson, 1944). As expected from the increased amount of 'direct' reacting bile pigment in the serum, some bilirubin was excreted in the urine (0.62 mg. per 24 hours) (method of With, 1942). Only a trace of porphyrin was found and a qualitative test for melanin was negative. Amino-nitrogen excretion was normal (31 mg. per 24 hours) and the amino-N-coefficient was 1.7.

STOOLS. The stools were of normal colour. The faecal urobilinogen excretion (average of two 24-hour collections) was 32.25 mg. per day, a value that is normal for this age group (method used for estimation, Schwartz *et al.*, 1944). The total bile pigment excretion (stools and urine) in 24 hours amounted to 37.1 mg. The haemolytic index (calculating a blood volume of 1,900 ml.) was 15. This normal value excluded an accelerated red cell destruction. The ratio of faecal to urinary urobilinogen was very low, 6.6:1 (the normal is about 100:1), showing that a much larger amount of urobilinogen was excreted by the kidneys than is normal.

'BROMSULPHALEIN' TEST. After intravenous injection of a dose of 5 mg. of 'bromsulphalein' (BSP) per kg. body weight, the retention in the blood 30 minutes later was 51%. On repetition of the test five weeks later, it was 48% (normal at this age 0.1-5%). The dye was detectable in the duodenal aspirate 45 minutes after the injection, whereas it normally appears within the first 15 minutes. The peak concentration of 66 mg. % in the duodenal fluid was reached after 70 minutes and two hours after the injection the concentration was still higher than 50 mg. %. Because of the difficulties in recording duodenal fluid volume it is not possible to give figures for absolute amounts excreted. In the urine 14.6% of the injected dose of BSP (125 mg.) was excreted in the first two hours after administration; the following portions contained progressively smaller amounts, but even 18 hours later the BSP concentration was still 1.9 mg. %. The results of the test are shown in Fig. 1. In addition chromatography of BSP metabolites in the serum 15, 30, 120 and 420 minutes after injection by the method of Carbone, Grodsky and Hjelte (1959) gave values of 5.3%, 5.4%, 17% and 26% respectively for BSP conjugates. This indicates an increase in the percentage of conjugated BSP concurring with a decrease in free BSP. In the bile, apart from free BSP, up to three BSP-conjugated were present, with Rf-values of 0.64, 0.57 and 0.40. From these findings an impairment of 'bromsulphalein' excretion is evident which seems to be caused not so much by a deficiency of conjugation as of secretion.

HIPPURIC ACID TEST. After intravenous injection of 1.5 g. benzoic acid the patient excreted 0.59 g. hippuric acid in the urine within the following one-hour period. In our experience this can be considered as a low normal result in a child of this age. Glycine conjugating ability seems not to be impaired to a great extent.

GLUCURONIDE FORMATION. N-acetyl-p-aminophenol (NAPA) was used as a substance to test the ability of the patient to form glucuronides. After oral or intravenous administration this substance is conjugated at the hydroxyl-group and excreted as glucuronide and sulphate in the urine. In adults the recovery within 24 hours is about 70 to 80% of the dose administered. Estimation of free NAPA in the serum and urine (Brodie and Axelrod, 1948) before and after hydrolysis with β -glucuronidase makes it possible to calculate the amount of NAPA

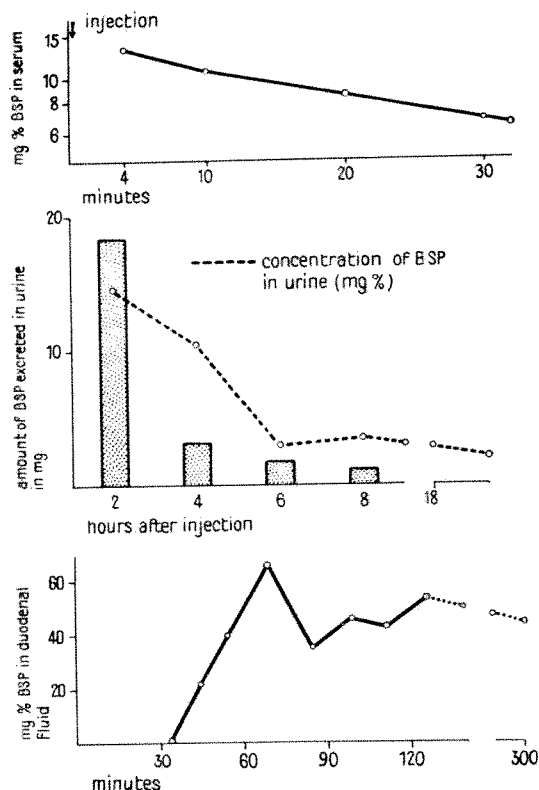


FIG. 1.—Bromsulphalein test; Upper part, concentration of 'bromsulphalein' in the serum after injection of BSP 5 mg. per kg. body weight, retention after 30 minutes, 51%; Middle part, amount of BSP excreted in the urine in four two-hour periods and concentration of BSP in the urine at various intervals after injection; Lower part, time of appearance and concentration of BSP in the duodenal fluid.

dase makes it possible to calculate the amount of NAPA conjugated with glucuronic acid (Vest and Streiff, 1959). Fig. 2 shows the results obtained with this test after intravenous injection of 240 mg. of N-acetyl-p-aminophenol. Retention in the serum was 7.6% after six hours (normal values are less than 10%). The curve showing the concentration of NAPA-glucuronide at various time intervals also takes a normal course. The girl excreted in the urine 72.7% of the dose injected within 24 hours. Of this 10.8% was in the free form, 45% conjugated with glucuronic acid and the rest with sulphate. Fig. 2 also shows the increase of glucuronic acid in the serum, which occurred after administration of NAPA. On the other hand this load did not influence the level of the serum bilirubin. The excretion of glucuronic acid (estimated by the method of Dische, 1947) in the urine amounted to 57 mg. per 12 hours during a control period. After the injection of the NAPA it rose to 177 mg. in the first 12-hour period and to 107 mg. in the second. These findings show that glucuronide formation is not deficient in this patient.

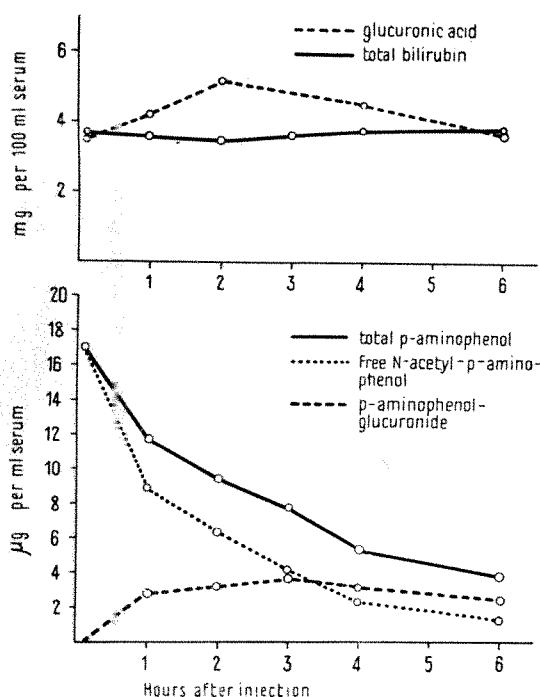


FIG. 2.—Test for the ability of the liver to form glucuronides; Upper part, concentration of glucuronic acid and total bilirubin in the serum at various times after injection of N-acetyl-p-aminophenol in a dose of 10 mg. per kg. body weight; Lower part, concentration of total p-aminophenol, free N-acetyl-p-aminophenol and p-aminophenol-glucuronide in the serum after the NAPA load.

RADIOGRAPHIC EXAMINATION. An oral cholecystography with four tablets of iopanoic acid (Cistobil 'Cilag') showed a well-filled gall bladder shadow. After ingestion of egg-yolk a contraction of the vesicle was clearly visible.

LIVER BIOPSY. A liver biopsy was performed, using a Menghini needle (Menghini, 1958). Histological examination* revealed normal liver tissue with an unaltered lobular hepatic structure. There was no increase in connective tissue in the portal tracts. The small bile ductules were not dilated and there were no bile thrombi in the bile capillaries. Glycogen was present in the liver cells in normal amounts. No abnormal pigmentation was seen either in the liver or in the Kupffer cells.

Discussion

This patient presented the following symptoms: a chronic jaundice with a serum bilirubin level between 4 and 7 mg. %, 50 to 70% of which reacted directly in the van den Bergh reaction; a normal

urobilinogen excretion in the stools but an increased amount of urinary urobilinogen and bilirubinuria; a markedly impaired BSP test, apparently without gross deficiency of conjugation; a low normal hippuric acid test; a normal glucuronide formation in a N-acetyl-p-aminophenol loading test; no evident signs of hepatocellular damage (normal flocculation-tests, normal prothrombin, normal transaminase, etc.), and a liver biopsy showing no alterations.

The absence of anaemia and increased erythropoiesis, the normal amounts of urobilinogen in the stools and the considerable concentration of 'direct' bilirubin in the serum indicate that the icterus is not haemolytic in origin.

An incomplete biliary obstruction should lead to reduced faecal bile pigment. In addition, some signs of liver damage would be expected after an obstruction of this duration, but were not present in this patient. The results of the liver biopsy and the prompt filling of the gall bladder on cholecystography also rule out a biliary obstruction.

Constitutional hepatic dysfunction (Gilbert's disease) can be excluded on the basis of normal glucuronide formation, the occurrence of direct bilirubin in the serum, the bilirubinuria and the abnormal BSP retention.

The case can be differentiated from chronic idiopathic jaundice (Dubin-Johnson; black liver jaundice) by the absence of the characteristic pigment in the liver cells and the filling of the gall bladder on oral cholecystography. The symptom of abdominal pain, so commonly found in the Dubin-Johnson disease, was also missing. It seems likely therefore that this girl belongs to the group of patients with non-haemolytic jaundice with conjugated bilirubin in the serum, first described by Rotor *et al.* (1948), where no pigmentation is present in the liver cells.

In contrast to the observations of Schiff *et al.* (1959) urinary urobilinogen excretion was increased in this patient. This corroborates Haverback and Wirtschafter (1960) who found high urinary urobilinogen levels in their two patients. Increased values of urinary bile pigment have also been found in chronic idiopathic jaundice with liver cell pigmentation (Dubin, 1958).

There is also some discrepancy with the findings of Schiff *et al.* (1959) with regard to the percentage of 'bromsulphalein' conjugates in the serum after BSP injection. They report 6% and 4% respectively at 45 and 90 minutes and we found 5.3% at 15 minutes, 5.4% at 30, 17% at 120 and 26% at 420 minutes. From this it would seem that the percentage of conjugates increases with time.

* Professor F. Roulet performed the examination of the liver biopsy specimen.

Perhaps, as with bilirubin, there is no deficiency of 'bromsulphalein' conjugation but mainly of secretion and this leads to the diminished removal rate from the plasma.

Nothing is known about the nature of the defect in this syndrome. Because an insufficiency of bilirubin glucuronide formation has been ruled out by all investigators, an impairment in the hepatic excretion of bilirubin glucuronide and a diminished uptake of bilirubin by the hepatic cells has been postulated (Schiff *et al.*, 1959). The familial occurrence makes it possible that the defect is a genetic error of metabolism. Males and females can be affected. The condition seems to be compatible with normal life as evidenced by the stationary state of health of Rotor's original patients (Rotor, 1960) more than 12 years after their initial examination.

Summary

A case of non-haemolytic, chronic jaundice in a girl, 7 years of age, is presented. The pertinent findings were onset of jaundice at 4 weeks of age, serum bilirubin levels between 4 and 7 mg. %, 50 to 70% of which gave a direct reaction, normal urobilinogen excretion in the stools, but increased urinary urobilinogen and bilirubinuria, 'bromsulphalein' retention of 50% after 30 minutes and low normal hippuric acid formation. The ability to conjugate with glucuronic acid in a N-acetyl-p-aminophenol loading test was normal. Oral cholecystography revealed a normal gall bladder. Other liver function tests were essentially normal. Liver biopsy showed a regular structure and appearance of the liver tissue without pigmentation. Chronic idiopathic jaundice (Dubin-Johnson syndrome) could therefore be ruled out and the patient was classified as a case of jaundice of the type described by Rotor *et al.* (1948).

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ARTERIOVENOUS ANEURYSM OF THE GREAT VEIN OF GALEN WITH HEART FAILURE IN THE NEONATAL PERIOD

BY

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The great cerebral vein of Galen extends from the junction of the two internal cerebral veins under the splenium of the corpus callosum to the commencement of the straight sinus. Arteriovenous aneurysms of this vein are rare congenital anomalies and only 22 cases have been found in a review of the literature.

Other types of cerebral arteriovenous aneurysms are not so unusual. Their true incidence has become more apparent following the widespread use of angiography. Mackenzie (1953) estimated their occurrence as 1% of all neurological admissions. By way of contrast Paterson and McKissock (1956) found no example of great cerebral vein aneurysm in 110 cases of cerebral arteriovenous aneurysm, and the same is true of the series reported by Olivecrona and Riives (1948), Mackenzie (1953) and Potter (1955). These vascular malformations are predominantly of two main types (Hamby, 1952). In the first type, there is a direct end-to-end connexion between an artery and vein, and in the second a network of poorly differentiated, non-capillary vessels intervenes between an artery and several veins, forming a mass of abnormal, dilated and tortuous vessels which sometimes goes by the name of 'angioma' but is not generally considered to be neoplastic. In both types veins not directly involved in the malformation may become enlarged and tortuous in response to the raised venous pressure. The great cerebral vein, however, only shows aneurysmal dilatation when there are one or more abnormal arterial vessels opening into it, its immediate tributaries or continuation. Other vascular malformations of the brain may coexist. These abnormal arterial vessels have arisen, in the described cases, from the posterior cerebral, posterior communicating, callosal and superior cere-

bellar arteries and from the choroid plexus of the third ventricle.

Local and general effects may be exerted on the cardiovascular system as in other varieties of arteriovenous aneurysm. The general effects may be difficult to detect. They include a variable increase in pulse pressure, tachycardia, apical systolic murmur and evidence of some enlargement of the heart. The literature contains reports of two babies who died of heart failure associated with a cerebral arteriovenous aneurysm not involving the great cerebral vein (Silverman, Breckx, Craig and Nadas, 1955) (Table 2) and three cases associated with an arteriovenous aneurysm of that vein (Table 1, Cases 11, 13 and 14). One of these infants had coarctation of the aorta as well.

The two cases reported here also died of heart failure associated with arteriovenous aneurysm of the great vein of Galen.

Case Reports

Case 1. S.F. was born September 15, 1959, by normal delivery at about 38 weeks' gestation. The birth weight was 2,240 g. and the head circumference was 33 cm. Respiration was established immediately.

Lower rib recession was noted 16 hours after birth and became more severe. The baby's extremities became cyanosed, peripheral pulsations were poor, there was a soft systolic murmur and the liver became enlarged. The respiratory rate rose to 70 per minute. This picture of respiratory distress and early heart failure was complicated by the occurrence of head retraction and opisthotonus 30 hours after birth followed by twitching and frank fits. Fontanelle tension was normal. Blood calcium was normal. Blood glucose levels were persistently low, 23 and 15 mg. % in the first 24 hours and never above 15 mg. % subsequently in spite of hourly glucose feeds. Lumbar puncture showed xanthochromic fluid under moderately increased pressure with 14,700 red and 75 white blood cells per cu. mm.

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Author	Case No.	Lesion and Arterial Supply	Presenting Symptoms or Signs
Steinheil (1895)	1	Left callosal artery; great and one small cerebral vein dilated; sacculated aneurysm on pedicle on great cerebral vein. Associated right frontal vascular malformation	Convulsions; left hemianopia
Jaeger, Forbes and Dandy (1937) Jaeger and Forbes (1946)	2	Huge dilated great cerebral vein pressing on aqueduct; large branches off both post. cerebral arteries into small cerebral veins; further vascular malformations	Internal hydroceph.; epistaxis,
Russell and Nevin (1940)	3	Atresia of int. jugular veins. Left post. cerebral artery branch to great cerebral vein; serpentine mass of vessels	Prominent face and neck veins; motor development; exoph. cranial bruit
Russell and Nevin (1940)	4	Sup. callosal art. and post. cerebral arteries, branches to great cerebral vein; aneurysm compressed aqueduct	Hydrocephalus; distended scalp
Alpers and Forster (1945)	5	Choroidal artery and post. cerebral arteries, branches to aneurysm of great cerebral vein	Mental retardation CNS signs; hydrocephalus
Oscherwitz and Davidoff (1947)	6	Tumour probably represented aneurysm of great vein of Galen and branches of circle of Willis	Headaches
Lumsden (1947)	7	Aneurysm on upper surface of tentorium attached to near great vein of Galen at junction of inf. sagitt. sinus and straight sinus; ? small artery from choroid plexus of 3rd ventricle	Fits; intraventric. and subarach. rhage
Boldrey and Miller (1949)	8	Branches of post. cerebral artery to aneurysm of great cerebral vein; pulsatile mass of vessels behind right mastoid	Hydrocephalus; dilated face, scalp pulsatile mass behind mastoid; subarach. haemorrhage
Boldrey and Miller (1949)	9	Post. communic. and post. cerebral arteries connected to great cerebral vein (angiogram)	Swollen face, eye veins; fatiguable
Wolfe and France (1949)	10	'At least one artery entered aneurysm of great vein of Galen'	Fits; CNS signs; int. hydroceph.
Pollock and Laslett (1953)	11	Post. cerebral and sup. cerebral arteries communic. with aneurysm of great vein of Galen and sag. sinus; also vessels from int. cerebral veins, most of supply vessels appeared to be thrombosed	Heart failure; large head
Petit-Dutaillis, Guiot and Berdet (1953)	12	Branches of post. cerebral arteries to aneurysm of great vein of Galen	Hydrocephalus
Clément, Gerbeaux, Combes-Hamelle, Pertuiset and Petranca (1954)	13	Feeding vessels to aneurysm of great cerebral vein not identified; much thrombus	Dyspnoea; increased muscular dysphagia; cyanotic attacks
Clément <i>et al.</i> (1954)	14	Post. cerebral arteries communicate with aneurysm of great cerebral vein; also 'very abnormal arterial distribution'	Failure to thrive; wasting; hy. dilated veins; cranial bruit;
Clément <i>et al.</i> (1954)	15	Personal communication on similar case	No details
French and Peyton (1954)	16	Anterior cerebral artery group communic. with great cerebral vein	Large head; failure to thrive retardation
French and Peyton (1954)	17	Abnormal mass of vessels on medial side. Right cerebral hemisphere, communicate with great cerebral vein, ant. callosal artery enlarged	Sub-arach. haemorrhages
French and Peyton (1954)	18	Arteriovenous malformation near pineal with rapid filling of great vein of Galen; abnormally large ? left ant. cerebral artery	Headache; slurred speech
French and Peyton (1954)	19	Branches of post. cerebral arteries into much dilated great vein of Galen	Headaches; subarach. haemorrh.
French and Peyton (1954)	20	Enlarged sup. great cerebral artery into large aneurysmal sac near pineal, draining into dilated great vein of Galen	Headaches; photophobia; lethargy; subarach. haemorrh. tal illness
Hirano and Terry (1958)	21	Branches of post. cerebral arteries seemed to end blindly in wall of aneurysm of great cerebral vein	Hydrocephalus, epistaxis, pro. pyrexia, ? cause
Gibson, <i>et al.</i> (1959)	22	Branches of post. cerebral artery to aneurysm of great cerebral vein, compressing aqueduct	Hydrocephalus
Claireaux and Newman (Case 1)	23	Arteriovenous aneurysm of both post. cerebral arteries and great cerebral vein	Heart failure, fits, opisthotonos
Claireaux and Newman (Case 2)	24	Arteriovenous aneurysm of right post. cerebral artery and great cerebral vein	Neck retraction

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THE GREAT CEREBRAL VEIN OF GALEN

at Onset	Age at Diagnosis	Associated Cardiovascular Signs	Surgery	Outcome
Child	49 yrs	—	—	Died
8 mths	4 yrs	Murmur and increased cardiac dullness after 'flu at 8 mths; bruit in neck at 27 mths, low blood pressure, anaemia; carotids dilated, also jugulars	Carotid ligation	Died
3 mths	17 mths	—	—	Died
2 mths	17 mths	None in life	Decompression	Died
6 yrs	18 yrs	—	Craniotomy	Died
6 yrs	27 yrs	Soft blowing systolic murmur	Craniotomy	Alive
4 mths	7 mths	—	—	Died
8 mths	16 mths	—	Carotid ligation; clipping of feeding arteries	Alive
Birth	15 yrs	—	Carotid ligation	Alive
3 yrs	21 yrs	—	Torkildsen's operation	Died
Birth	4 days	Heart failure	—	Died
4 mths	4 mths	—	—	Alive
? Birth 0 days	1 mth	Heart failure	—	Died
? 3 wks	7 mths	Heart enlarged; coarctation of aorta	—	Died
Infancy	—	—	—	Died
2 mths	21 mths	—	Craniotomies; clipping of feeding arteries	Alive
?	12 yrs	—	Clipping of feeding arteries	Alive
?	22 yrs	—	Clipping of feeding arteries	Alive
?	14 yrs	—	—	Alive
?	43 yrs	—	Craniotomy	Alive
5 mths	28 mths	—	—	Died
6 mths	4½ yrs	—	Anastomosis of spinal theca to peritoneum	Died
6 hrs	4 days	Cyanosis, systolic murmur, neck pulsations, heart failure	—	Died
4 hrs	16 days	Cyanosis, systolic murmur, neck pulsations	—	Died

— Nil or not mentioned

TABLE 2
HEART FAILURE ASSOCIATED WITH CEREBRAL ARTERIOVENOUS ANEURYSM NOT INVOLVING GREAT CEREBRAL VEIN OF GALEN

Author	Case No.	Lesion and Arterial Supply	Presenting Symptoms or Signs	Age at Onset	Age at Diagnosis	Associated Cardiovascular Signs	Surgery	Outcome
Silverman <i>et al.</i> (1955)	1	Right cerebral hemisphere almost replaced by massive vascular network penetrating right frontal bone; right middle and post. cerebral arteries gave branches to communicate with dilated sup. sagitt. sinus	Dyspnoea; cyanosis	4 hrs	1 day	Systolic murmur; right carotid thrill; cardiac enlargement and failure	—	Died
Silverman <i>et al.</i> (1955)	2	Large cirsioid aneurysm between middle cerebral artery and sigmoid sinus; large tortuous vascular channels	Respiratory distress; cyanosis; shrill cry	30 hrs	3 days	Systolic murmur; venous congestion; cardiac enlargement	—	Died

The cerebrospinal fluid glucose level was 30 mg. %. The opisthotonus improved markedly after the lumbar puncture but relapsed. The fits, some left sided, recurred. Neck pulsations became very vigorous. Venous congestion, further enlargement of the liver and peripheral oedema developed. Digitalization caused only a transient and partial reversal of these signs. An electrocardiogram showed digitalis effect and increased P waves and some evidence of left as well as of right ventricular enlargement. The baby died on the fourth day, in heart failure. Blood glucose levels had shown no sign of rising.

ELECTROENCEPHALOGRAM. 'The pattern of this record is that of a full term normal baby when awake and sleeping. There is perhaps a little more rhythmic activity at 15 c./sec. than usual but this may be accounted for by the prematurity. This activity is mostly seen when the baby is awake and is up to 25 μ V in amplitude. When the baby is asleep there are repeated single or multiphasic sharp waves up to 250 μ V in amplitude and up to duration 0.5 sec. These slow sharp waves are unilateral and occur simultaneously over all areas of the head and about equally on both sides' (Dr. Ruth Harris).

RADIOLOGY. Skull radiograph revealed no abnormality; chest radiograph showed only moderate cardiac enlargement.

NECROPSY. The body was that of a small male infant weighing 2,150 g. The dura mater and pia arachnoid were healthy. The brain (333 g.) was firm. The torcular Herophili was greatly enlarged and contained firm clot. Clot was also present in the superior and inferior longitudinal sinuses, the transverse sinuses and the jugular bulbs. The jugular veins appeared to be normal. At the base of the brain a large aneurysm was found. This was largely composed of a grossly distended great cerebral vein of Galen which communicated anteriorly with both posterior cerebral arteries and posteriorly with the distended torcular (Fig. 1). The aneurysmal sac measured 2.2×1.5 cm. The arterial communication was complex. The basilar

artery divided anteriorly into the right and left posterior cerebral arteries in the usual manner. The right posterior cerebral artery then divided immediately into four and these reunited after passing downwards and backwards for a distance of 3 cm. The thick vessel thus formed then subdivided again before uniting with the aneurysm (Fig. 2). The left posterior cerebral artery divided into three and the branches joined the anterior part of the aneurysm. The great cerebral vein after receiving the internal cerebral veins expanded into a thick-walled sac. This sac received both posterior cerebral arteries and these passed backwards to join the torcular Herophili. The aneurysm had a bulbous anterior portion, a narrow neck and a fusiform body. The cerebral veins were not distended. The lower portion of the

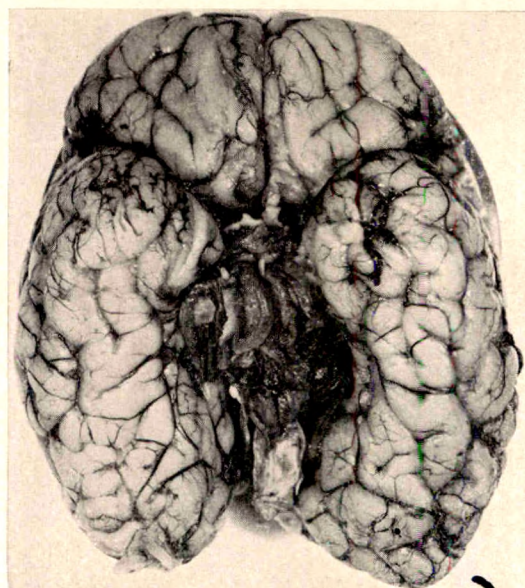


FIG. 1.—Case 1, brain; the inferior surface is exposed to show the aneurysm of the great cerebral vein and the abnormal communications with the posterior cerebral arteries.

aqueduct of Sylvius was of normal calibre and the fourth ventricle was not distended. The anterior surface of the cerebellum was hollowed in the region of the aneurysm. The brain was congested.

The pericardium was clear and glistening and there was a moderate quantity of clear, yellow fluid in the pericardial sac. The heart was enlarged as a result of dilatation of the right atrium and right ventricle. Both chambers contained a large amount of blood clot. The foramen ovale and ductus arteriosus were patent. The valves and great vessels had a normal appearance.

The larynx, trachea and bronchi were healthy. The lungs were congested and some subpleural haemorrhages were present. On slicing a few haemorrhagic areas were noted. The stomach and bowel were healthy. The liver (52 g.) and spleen (5 g.) were not enlarged. The genito-urinary tract was healthy and the endocrine glands showed no abnormality. Supernumerary digits were present on the lateral border of each hand. There was a complete extra finger on the left hand and a rudimentary one on the right. The fifth toe of the right foot was bifid.

HISTOLOGY.

Lungs. The pleura was healthy. The lungs were congested but quite well expanded. Some patchy haemorrhage was present. In some areas the alveolar ducts and alveoli were flooded with red cells. The bronchi were healthy. There was no pneumonia.

Aneurysm. A section was taken through the most dilated portion of the great cerebral vein. The lumen contained fibrin thrombus. The wall was quite thin and there was evidence of degeneration. No intima was recognized.

Left Posterior Cerebral Artery. The lumen was

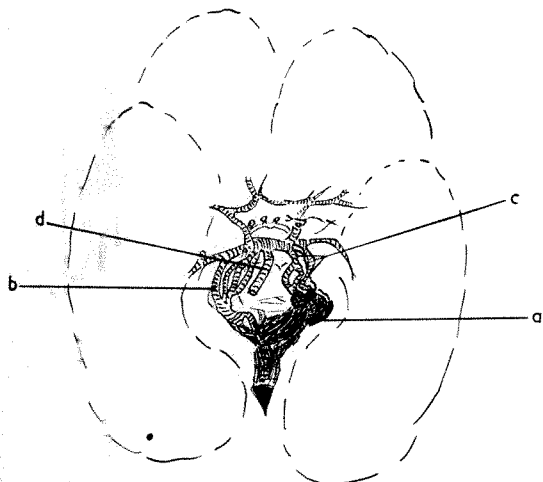


FIG. 1.—Case 1, brain; outline drawing to show (a) aneurysm of great cerebral vein, (b) right posterior cerebral artery with abnormal branching, (c) left posterior cerebral artery, (d) basilar artery.

occluded by fresh thrombus which showed no evidence of organization. The vessel was distended as a result of the enclosed thrombus. The wall showed no degenerative change.

SUMMARY. Cerebral arteriovenous aneurysm; intra-pulmonary haemorrhage; supernumerary digits on each hand and bifid right fifth toe.

Case 2. The mother, 23 years of age, para 0 had bilateral active tuberculosis and during pregnancy had to be treated for pyelonephritis resulting from infection with *Escherichia coli*. She went into labour at term and the infant was delivered spontaneously. The first stage of labour lasted 18 hours 30 minutes and the second stage 30 minutes. There was a vertex presentation.

The infant was a male and weighed 3,715 g. at birth. The head circumference was 32.5 cm. The infant's condition was good and he cried immediately. There was no peripheral cyanosis but cardiac pulsation was noted to be vigorous and there was strong arterial pulsation in the neck. A systolic murmur was heard over the apex. On radiological examination the heart was seen to be enlarged. One week after birth cyanosis was observed and there was slight pitting oedema of the feet and legs. The pulse rate was 160 per minute and respirations 40 per minute. A diagnosis of congenital malformation of the heart was made. Further radiological examination on the 11th day showed an increase in the size of the heart. Cyanosis became more marked and neck retraction was noted. The infant's condition steadily deteriorated and he died 16 days after delivery.

NECROPSY. The body was that of a well developed male infant and weighed 3,345 g. The sternum was prominent. The falx and tentorium were intact. The brain (400 g.) was very soft and markedly congested. The great cerebral vein was replaced by a large saccular aneurysm 4.5 cm. in length and 2 cm. in diameter. This aneurysm was attached to the junction of the falx with the tentorium. It communicated anteriorly with the right and left internal cerebral veins and with the right posterior cerebral artery. The cerebral veins were engorged but not thrombosed. There was slight dilatation of the lateral ventricles and of the third ventricle which contained clear cerebrospinal fluid. The aqueduct was patent and the fourth ventricle was of normal size. A small amount of subarachnoid haemorrhage was present over the cerebellum. On slicing the aneurysmal dilatation of the great cerebral vein was found to contain organized thrombus.

The pericardium was clear and glistening, there was a small quantity of clear, straw-coloured fluid in the pericardial sac. The heart was considerably enlarged, chiefly as a result of hypertrophy and dilatation of the right atrium and right ventricle. The interventricular septum was intact and very broad. Thick post-mortem clot was present in the right atrium. There was no structural abnormality of the heart valves or of the great vessels. The foramen ovale was closed. The ductus



FIG. 3.—Case 2, heart; right ventricle opened to show gross myocardial hypertrophy.

arteriosus was narrowly patent. The venous drainage was normal (Fig. 3).

The larynx, trachea and bronchi were healthy. The lungs were moderately well expanded and congested. Some patchy basal consolidation was found.

The stomach and bowel showed no pathological change. The liver (149 g.) was enlarged and congested. The spleen (15 g.) was large and very congested. The genito-urinary tract was healthy. The endocrine glands showed no abnormality.

HISTOLOGY.

Lungs. The pleura was healthy. The lungs were congested and some haemorrhage had occurred into the alveoli. In sections from the lower lobes there were widespread areas of consolidation. Many alveoli and alveolar ducts contained a dense cellular exudate composed of polymorphonuclear leucocytes and histiocytes. Some small bronchi contained a similar exudate. Immediately beyond the consolidated areas there was a zone of overdistension of alveoli and alveolar ducts. The appearance was that of a bronchopneumonia.

SUMMARY. Arteriovenous aneurysm of great cerebral vein; hypertrophy and dilatation of the heart, and terminal bronchopneumonia.

Discussion

Aneurysm of the great vein of Galen differs clinically from the more common types of cerebral

arteriovenous aneurysm in the early onset of symptoms and the apparently greater frequency of serious cardiovascular effect. Moreover, hydrocephalus is a commonly associated feature probably as a result of pressure by the aneurysm on the aqueduct of Sylvius. Hydrocephalus was not present in either of our patients. This is probably the result of the comparatively short duration of any pressure effects. In both the brains we examined, the aqueduct was still widely patent although slightly distorted. Similarly, we found no thickening of the wall of the aneurysm and no evidence of mucinous degeneration such as was reported by Russell and Nevin (1940). This lack of degenerative change appears to indicate that the dilatation of the vein is not secondary to a degeneration of the vessel wall as these workers suggested. In some instances (Russell and Nevin (1940), Case 1) a genuine arteriovenous aneurysm and a vascular hamartoma are present together. In our Case 1 there was some very peculiar branching of each posterior cerebral artery before union with the great cerebral vein took place, but in neither case was there any evidence of a network of fine vessels which might be designated a hamartoma.

In the 24 cases listed (Table 1) symptoms had commenced in infancy or childhood in two, at less than 6 months in 12, at 6 months to 1 year in three, at 1 to 10 years in two and in adult life in only one case. The date of onset was not stated in four cases who were diagnosed at 12, 14, 22 and 43 years respectively. In the more usual type of cerebral arteriovenous aneurysm or 'angioma' symptoms are more usually delayed until the second decade or later (Olivecrona and Riives, 1948; McKissock, 1950; Mackenzie, 1953). Cases presenting in infancy or childhood are proportionately rare.

In great cerebral vein aneurysms the symptomatology includes dilated face and scalp veins, proptosis, fits, headache, the effects of subarachnoid and intraventricular haemorrhage, mental retardation, focal signs in the central nervous system and failure to thrive. General circulatory effects were noted in six of the 24 cases and heart failure appeared to be the primary cause of death in five of these. One had coexisting coarctation of the aorta. Hydrocephalus developed in nine cases, two more having a 'large head'.

The course at first sight appears to be short. Death occurred under the age of 2 in nine, under the age of 5 in three and at 18, 21 and 49 years in a further three. Only one of seven cases reported before 1947 and before angiography was performed for diagnosis was alive at the time of reporting. This contrasts with eight of the remaining patients

and suggests that the prognosis may not really be so gloomy. Death was associated with internal hydrocephalus, fits, haemorrhage, craniotomy and heart failure.

Diagnosis was made by angiography, at necropsy or at operation. An intracranial bruit was not listened for in the two cases reported here and, when sought in other cases, has only sometimes been detected. The association of local or general cardiovascular abnormalities with a suspected intracranial lesion is characteristic of these malformations. The retinal veins appeared normal in the two cases described here.

Treatment is medical and surgical. The former has little to offer. It cannot influence the aneurysm nor the shunt, and the treatment of associated heart failure has been quite unsuccessful. Surgery has had some successes. It was carried out in 10 cases. Carotid ligation, attempts to relieve hydrocephalus and simple craniotomy had poor results. Surviving patients had undergone the following procedures: Craniotomy only, two; carotid ligation, one; carotid ligation with subsequent clipping of arteries feeding the aneurysm, one; clipping of feeding arteries, three. French and Peyton (1954) consider the condition operable if the arterial supply to the aneurysm can be demonstrated by angiography. Occlusion of the feeding arteries (which appears to have taken place spontaneously in Case 21) may not influence associated hydrocephalus, but will probably prevent pressure effects from further enlargement. It must also reduce the likelihood of haemorrhage and should correct the effects of the shunt on the cerebral circulation and on the heart itself. The youngest patients in whom feeding arteries were clipped were both under 2 years of age. Both survived but neither had been in heart failure. It is doubtful whether any of the infants who died of this complication could have been saved, but it is just possible that carotid occlusion might have improved their circulatory status temporarily.

The cardiovascular effects associated with arteriovenous aneurysms may be extensive. They have been reviewed by Lewis and Drury (1923), Holman (1923, 1924), Reid (1925a, b), McGuire (1935) and Potter (1955). Several authors had noted cardiac enlargement in cases of cerebral arteriovenous aneurysm, but Schmitt (1920) appears to be the first to have stressed this feature. He wrote: 'Hypertrophy of the left ventricle . . . is often found in the more advanced stages of cerebral arteriovenous aneurysm' and 'the combination of brain disorder with cardiovascular symptoms is very important in the diagnosis of cerebral arteriovenous

aneurysm'. He further mentions the dilatation of arteries to the head. In subsequent accounts the effects on the cardiovascular system are not always mentioned. Their incidence is therefore difficult to assess. Cushing and Bailey (1928) and Dandy (1928) found definite cardiac enlargement lacking in their cases even though it might have been expected in some on the grounds of size of aneurysm, location and duration of symptoms. Brock and Dyke (1932) found cardiac enlargement in four of five cases of cerebral arteriovenous 'angioma'. Ray (1941) noted partly reversible cardiac enlargement in one of 16 cases. Shenkin, Spitz, Grant and Kety (1948) found it in two cases investigated to determine the cerebral blood flow, which was much increased. Silverman *et al.* (1955) record two infants who died in heart failure from this cause in the newborn period and Paterson and McKissock (1956) noted cardiac enlargement in nine of their series of 110 cases. Aneurysm of the great vein of Galen does not feature in these reports but enlargement has occurred in four reported cases, three of whom died in heart failure, as did the two additional babies reported here. The very marked effect on the cardiovascular system exerted by the arteriovenous shunt is indicated in Case 2 where there is enormous hypertrophy of the wall of the right ventricle which was three times the normal thickness for this stage of development.

Hypoglycaemia has not been previously described in this context. It may have been coincidental, but the proximity of the aneurysm to the floor of the fourth ventricle is suggestive.

The cases presented here and the review of the literature make it apparent that cerebral arteriovenous aneurysms may present with symptoms referable to the cardiovascular system. The possibility of such lesions should be considered when a vigorous cardiac impulse and increased neck pulsations are associated with signs of meningeal irritation or convulsions. Respiratory distress may mask these features in the newborn period. If it is possible to confirm the diagnosis by angiography, surgery may offer a chance of successful treatment. Untreated, the patient may die in the newborn period from cardiac failure, or subsequently from the effects of hydrocephalus and haemorrhage.

Summary

Two cases of arteriovenous aneurysm of the great vein of Galen are reported. Both were infants who died in the newborn period of heart failure. Both exhibited neck rigidity in addition to cardiovascular signs. One infant had persistent hypo-

glycaemia. Clinical features of this type of arteriovenous aneurysm are reviewed and it appears that hydrocephalus and severe cardiovascular effects are commoner than in the 'angioma' type of cerebral arteriovenous aneurysm. Surgery appears to hold out the possibility of cure in some cases, provided that diagnosis and angiography anticipate the potentially rapid decline of such patients.

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Addendum

Since this paper has been sent to the press, two additional cases of cerebral arteriovenous fistula associated with heart failure have been reported by Glatt and Rowe (1960).

TWO CASES OF RETICULOENDOTHELIOSIS— LETTERER SIWE SYNDROME

BY

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Diseases characterized by proliferative changes in the reticulo-endothelial system, other than the leukaemias and specific infections such as tuberculosis and typhoid fever, give rise to three main syndromes in children, but there are many atypical and intermediate forms. Originally described as three separate conditions, these syndromes, namely Letterer-Siwe disease, Hand-Schüller-Christian syndrome, and 'eosinophilic granuloma' of bone are now believed by many authorities to have a common aetiology, as yet unknown, and basic pathology. Van Creveld (1951) is of the opinion that a distinction between the first two is unnecessary and at times impossible, and clinical pictures occupying intermediate positions between them and even sharing features of the infectious reticuloses have been described; Siwe (1949) on the other hand, maintained that they were pathologically distinct. Those authors who accept the theory of unity of Letterer-Siwe disease and Hand-Schüller-Christian syndrome do so on the assumption that lipoid storage would develop in the former if the disease were protracted; moreover, sequences of the three morbid pictures in one patient on consecutive biopsies have also been described by Bartels (1947), Wentholt and Hadders (1949), Love and Fashena (1948), and Parkinson (1949). That this sequence of events is not always followed has been shown elsewhere and is further demonstrated by the protracted course of one of the cases to be described, but in it account must be taken of the modifying effects of steroids.

Considerable evidence is accumulating on the value of ACTH and cortisone in the treatment of the three syndromes, particularly of the subacute and chronic forms of the Hand-Schüller-Christian syndrome. Karlen (1952) reported disappearance of hepatosplenomegaly and exophthalmos in an 18-month-old girl on cortisone therapy, but relapse occurred when the treatment was stopped on account of severe oedema, and the patient died. Røjel and

Lund (1958) described a boy with Hand-Schüller-Christian syndrome aged 14 months at onset, but not diagnosed till 3 years and 9 months, who was pronounced cured after three years' treatment with ACTH and cortisone, but he was observed for only three months after cessation of treatment, and had received x-ray therapy also.

Sewell (1954) presented a girl of 3 years 10 months to the Royal Society of Medicine who had shown histological features of eosinophilic granuloma of bone and later of Hand-Schüller-Christian syndrome with clinical improvement on cortisone after failure to respond to Xrays; and Flosi, Assis, Coelho Neto, Bloise, Ulhôa Cintra and Barros (1959) described a complete remission after four years almost continuous treatment with cortisone and ACTH in a boy diagnosed as suffering from Hand-Schüller-Christian syndrome when 1 year old, the symptoms having commenced about four months previously. After a year's treatment with cortisone followed by ACTH, maximum dosage 75 mg. daily, he developed marked features associated with Cushing's syndrome at which stage treatment was gradually reduced; but bone lesions which were already resolving continued to improve and eventually disappeared after four years' treatment.

Bearing this evidence in mind, it is necessary to remember the occurrence of spontaneous remission which is the usual outcome in patients with eosinophilic granuloma of bone and is also well recognized in the Hand-Schüller-Christian syndrome.

Moreau (1930) found nine cases of spontaneous recovery amongst 34 cases of Hand-Schüller-Christian syndrome described in the literature, and while Letterer Siwe disease is generally fatal, spontaneous recovery is possible (Lightwood and Tizard, 1954). Recovery from this disease induced by cortisone was described by Cox (1955), and Orrild and Lunding (1953) reported a case of Letterer Siwe disease apparently cured by ACTH.

The object of this communication is to place

on record two further cases of reticulosis and to describe the effect of prolonged steroid therapy in one, the other dying before treatment was properly instituted.

Case Reports

Case 1. J.E. was 25 months of age when admitted to hospital in April, 1955, with a history of malaise following an upper respiratory infection two weeks previously. For a week he had been drowsy and listless, inclined to vomit and was thought by his mother to be having headaches. A few days before admission puffiness was noticed around the eyes, which for the past 24 hours had protruded.

He was the second child of healthy parents, born at term; his birth weight was 7 lb. 11 oz. He was breast fed for one month only, but he made good progress and his only illness had been an attack of otitis media treated with penicillin one year previously. The family history was uneventful.

EXAMINATION. Temperature 99.8°F. He had a pale, puffy face and proptosis of both eyes, the right slightly more than the left. In addition to the puffiness of the eyelids there were also symmetrical, fairly well defined swellings in the temporal fossae (Fig. 1) and an indefinite swelling in the right parietal region. The tonsils were enlarged but not inflamed; cervical and axillary glands were moderately enlarged; the heart and lungs appeared normal; liver and spleen were not felt. The optic fundi showed no abnormality, and the cerebrospinal fluid was also found to be normal. A blood count was reported Hb 86% (12.7 g.); colour index, 1.04; W.B.C.s, 6,000/c.mm. (polymorphs 40%, lymphocytes 60%).

A tentative diagnosis of Hand-Schüller-Christian syndrome was made, but there was no polyuria and urine specific gravity reached 1.016. Moreover, radiographs of skull, thorax and long bones revealed no abnormality apart from opacity of both antra and ethmoid cells. Because of this finding and the fact that his temperature fluctuated between 100° and 101° F. the possibility of



FIG. 1.—Showing puffiness of eyelids and symmetrical well-defined swellings in temporal fossae.

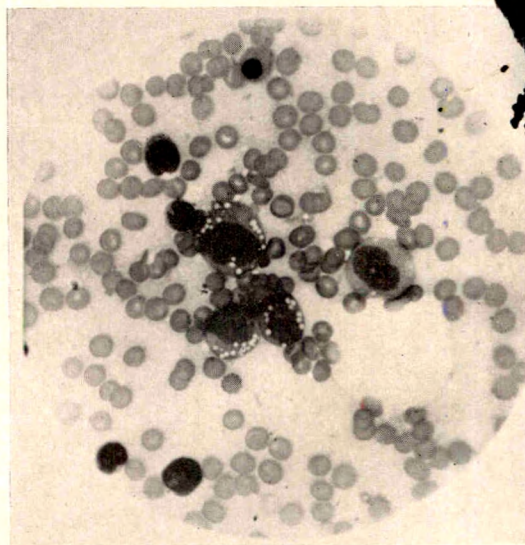


FIG. 2.—Blood smear showing vacuolated macrophages. ($\times 480$.)

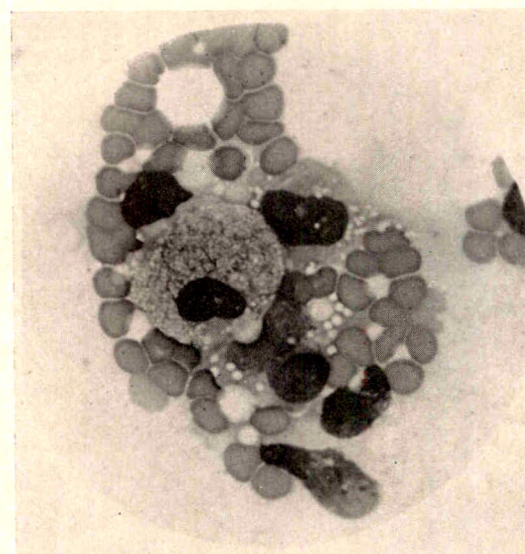


FIG. 3.—Bone marrow showing a foam cell and vacuolated cells. ($\times 650$.)

ethmoiditis was considered, and treatment with antibiotics started. No improvement followed, however, and six days after admission chemosis of both conjunctivae and retinal oedema appeared; there was no real papilloedema. A second blood count showed a fall in Hb to 78% (11.5 g.) and vacuolated cells were found in the smear (Fig. 2). The E.S.R. was 6 mm. in one hour, platelets 14,000/c.mm. and bleeding time more than 12 minutes. Bone marrow aspiration showed a normocellular marrow containing 'foam cells' (Fig. 3) similar

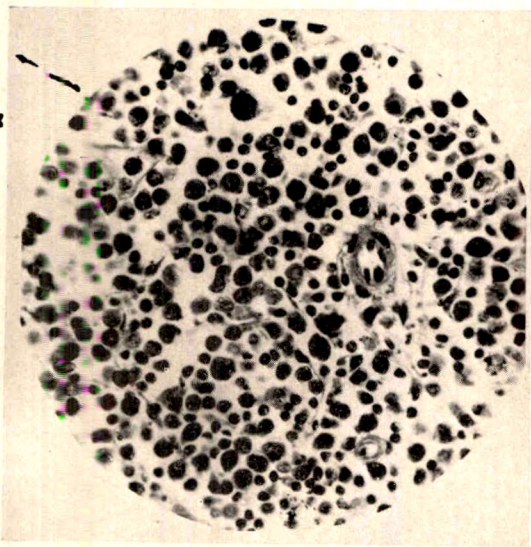


FIG. 4.—Gland infiltrated with reticulum cells. (H. and E. $\times 150$.)

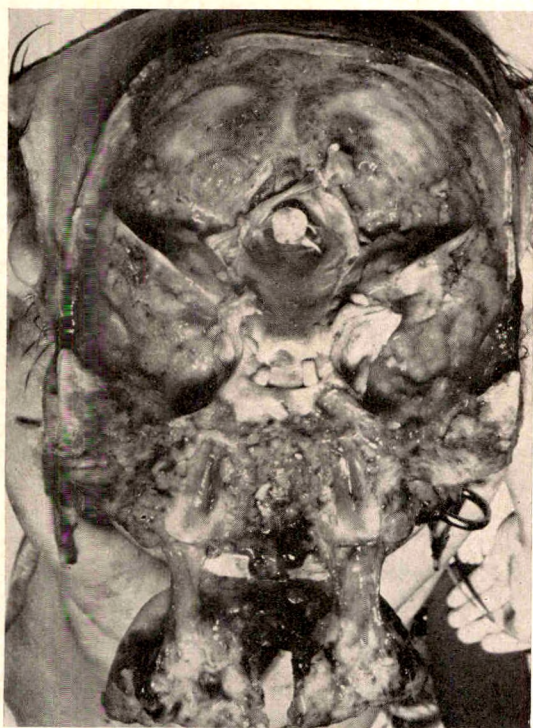


FIG. 5.—Horizontal section through skull showing tumour-like mass in anterior fossae.

to those occurring in the Hand-Schüller-Christian syndrome; gland biopsy showed complete replacement of the normal architecture by sheets of pale reticulum cells, but no 'foam cells' (Fig. 4).

Cortisone was now added to the treatment but the child's condition deteriorated rapidly. Spontaneous bleeding occurred and he became progressively more anaemic in spite of blood transfusion.

He appeared to be quite blind for several days before he died, two weeks after admission to hospital.

NECROPSY. A mass of tumour-like tissue in the anterior fossae of the skull, in the orbits and air sinuses, and invading the upper part of the nose via the cribriform plate was revealed (Fig. 5), but the pituitary fossa appeared intact. A large tumour was found in the lower end of the right femur (Fig. 6). The thoracic and abdominal glands were all enlarged and invaded, and there were small deposits in the heart, kidneys and wall



FIG. 6.—Large tumour in lower end of right femur.

of the small intestine. The liver and spleen appeared normal macroscopically and the lungs showed hypostatic changes only, but histological deposits were noted in lungs, spleen, liver, pancreas, ribs and tonsils. The pituitary gland was normal on section apart from tumour around the capsule. The microscopic picture was of uniform infiltration with sheets and trabeculae of mononuclear cells with pleomorphic nuclei and scanty eosinophilic cytoplasm. No foam cells were found in any of the necropsy sections and no cholesterol was demonstrable in the cells by histochemical techniques.

Case 2. J.C. was 5 years old when admitted in February, 1957, with a history of malaise, loss of appetite, limb pains and irregular fever following an upper respiratory infection one month earlier. He was the third and youngest child of healthy parents, born at term; his birth weight was 6 lb. 10 oz. He was breast fed for three months and his progress had been entirely normal. The family history was uneventful.

EXAMINATION. He was a fretful, pale, ill-looking child, with several small bruises and a few petechiae on the trunk. His tonsils were large and unhealthy and tonsillar glands were palpable; there were small discrete glands in axillae and groins, and his liver was easily palpable, his spleen being just felt. No nodules or bony swellings were found, but he resented examination because of muscle tenderness. A tuberculin patch test was negative. Radiographs showed possible erosion of one rib, but no lesion in skull, spine or long bones. Haematological examination revealed Hb 64%, W.B.C.s less than 1,000/c.mm. (polymorphs 11%, lymphocytes 87%, monocytes 2%, platelets scanty); bleeding time more than 15 minutes. Marrow puncture demonstrated the presence in the marrow of many histiocytic cells with slightly foamy cytoplasm, suggesting a diagnosis of Letterer Siwe syndrome. ACTH in a dosage of 40 units daily was started four days after admission together with penicillin, and a blood transfusion was given the following day, Hb having fallen to 58%; a blood film at this time showed many smear cells.

After four days' treatment the child's general condition had improved remarkably; he lost his muscle pains and became much more cooperative, accepting drugs by mouth which he had previously refused, so prednisolone 12.5 mg. t.d.s. was substituted for ACTH intramuscularly. He was given another blood transfusion as his Hb had only risen to 66% and four weeks after the beginning of treatment he was symptom-free, had no palpable glands, no obvious enlargement of the spleen and a second marrow puncture showed a normal picture apart from a very few of the abnormal cells originally seen. His liver, however, was still palpable two finger breadths below the costal margin. He had become moonfaced, and his weight had increased by 8 lb. over his admission weight of 29 lb. 5 oz., so prednisolone was reduced to 10 mg. t.d.s. and on this dosage he was discharged to the Out-patient Department at the end of March, his Hb at that time being 75% and W.B.C.s 4,600/c.mm. Dr. Bodley Scott who had seen this

child in consultation reported: 'I agree that the primitive cells found in the bone marrow and displacing almost all the normal cells are quite unlike the usual 'blasts' of acute leukaemia. They have irregular nuclei of the reticulum cell type and some have a foamy cytoplasm. Together with the x-ray changes they support a diagnosis of 'Letterer Siwe syndrome'.'

He was seen frequently in the Out-patient Department and he remained well but exhibited the appearance of florid Cushing's syndrome. His haemoglobin was maintained and he had no enlargement of liver, spleen or glands. He complained of pain in one ankle but nothing abnormal was found, and as he was markedly overweight (46 lb.) his dose of prednisolone was reduced slowly after two months on 30 mg. daily, until he was taking only 5 mg. a day at the beginning of July. He lost 5 lb. in weight, felt well and began to grow. His Hb was still 96% and blood picture normal; B.P. 110/65 mm. Hg. Prednisolone was again reduced in August to 2.5 mg. daily and continued at this level until in September his testes were noticed to be rather hard and insensitive, and a week later his parotid, submaxillary, axillary and inguinal glands were visibly enlarged and felt firm. Liver and spleen were still not palpable and Hb was 90%, but smear cells were again seen in the blood film (September 24, 1959), as well as a few atypical mononuclear cells. He was admitted on October 1, 1957, for biopsy of a gland and the dose of prednisolone was increased to 10 mg. daily, but he did not improve. The report on the biopsy specimen stated: 'The normal structure of the lymph node has been destroyed, being replaced by a uniform proliferation of medium sized oval cells with scanty eosinophilic cytoplasm and reticular nuclei. The capsule is invaded at one point, and the abnormal cells are infiltrating the fat outside the node. Mitoses are numerous. I regard this tumour as a lymphosarcoma.'

Prednisolone therapy was continued in the same dosage but muscle pains returned and a few histiocytic cells were again seen in the peripheral blood in mid-October, at which time the dose was increased to 30 mg. daily. Rapid weight gain resulted but the symptoms progressed and by the middle of November he was unable to walk on account of general stiffness and tenderness. Radiographs of ribs, pelvis and long bones (November 15, 1957) showed no abnormality.

His condition deteriorated steadily, he became anaemic and leucopenic once more, and developed scattered bruises and petechiae. His weight fell steadily to 36 lb. on December 10, in spite of progressive increase in the dose of prednisolone up to 120 mg. daily and blood transfusion, and by December 20, 1957, his liver had enlarged to three fingers-breadth below the costal margin and spleen and glands were easily palpable. Radiographs (December 19, 1957) showed a little periosteal infiltration in several long bones and slight generalized osteoporosis. He was discharged home for Christmas and re-admitted (December 30, 1957) in severe pain, extremely weak and bleeding from the nose; Hb 40%, W.B.C.s too scanty to count. He was again transfused and another bone marrow puncture was attempted, but

was unsuccessful because he bled too much. For the same reason biochemical investigations were not undertaken, but on January 3, 1958 potassium chloride 1.5 g. daily by mouth was started on an empirical basis because of high dosage of prednisolone, general weakness and abdominal distension, steroid therapy being maintained unaltered.

A few days later he was much improved, moving his legs without pain and no longer bleeding spontaneously. At the beginning of February he was once more on his feet, and even running a little. His haemoglobin rose steadily without further transfusion, his white cell count became normal and no histiocytes or smear cells were seen in the blood film; his spleen was no longer palpable but his liver and preauricular glands were just felt.

He was discharged home on February 12, 1958, still on 120 mg. prednisolone daily, and he felt well, but he ate enormously and gained nearly a stone in weight in the next three weeks, reaching 50 lb. His blood pressure rose to 150/90 mm. Hg, having been around 110/60 mm. Hg previously. By the end of March he was too tired to walk and complained of pain in the back, so he was readmitted on March 21, 1958, still with all the signs of florid Cushing's syndrome (Fig. 7). Radiographs showed marked osteoporosis of lumbar vertebrae with flattening and compression of most of the vertebral bodies (Fig. 8) and also slight deformity of the neck of the left femur. Apart from his high colour, obesity and loss of lumbar curve the child seemed well and showed no sign of the original disease. There was now no

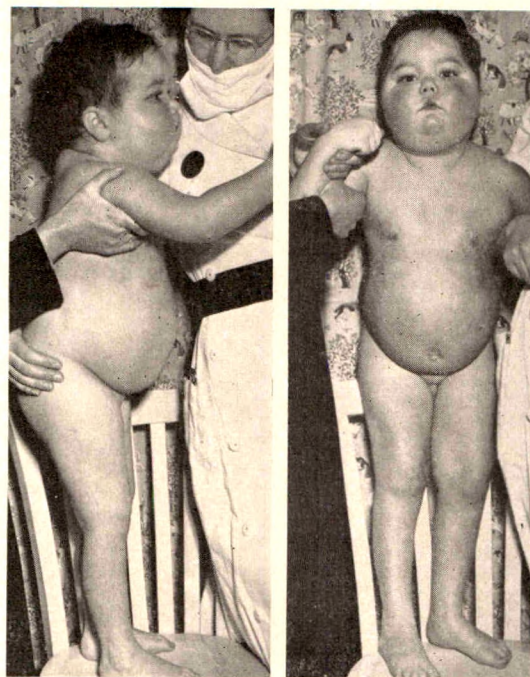


FIG. 7.—Showing signs of florid Cushing's syndrome.

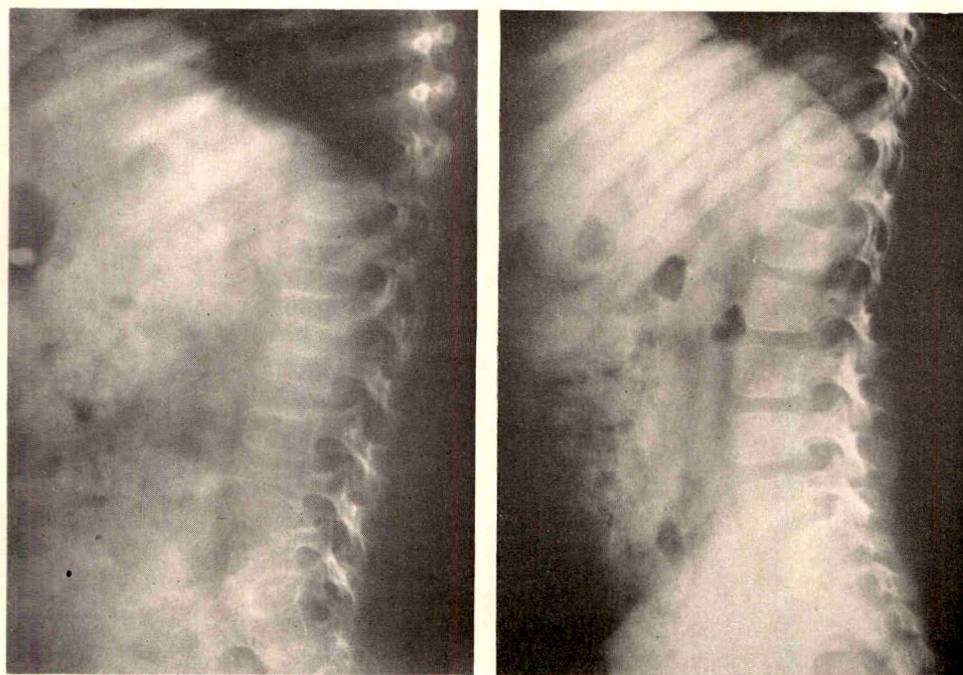


FIG. 8.—Lumbar spine showing osteoporosis, compared with spine of same patient six months earlier.

anaemia and marrow puncture showed no evidence of any haemopoietic disorder, normal polymorphs being most plentiful, granulocyte precursors numerous, primitive and abnormal cells absent.

He was fitted with a plaster bed and his dose of prednisolone was gradually reduced being combined with ACTH. He appeared well; ketosteroid excretion was satisfactory and blood pressure 120/90 mm. Hg. On May 7, on a dose of prednisolone 20 mg. b.d. and ACTH 40 mg. daily, he was found to have a number of large, slightly tender glands in the neck and a nodule on the occiput, but liver and spleen were still not palpable. On May 12 another marrow biopsy was obtained which showed the marrow grossly infiltrated by large pleomorphic reticulum cells (Fig. 9) the nuclei of which had a coarse chromatin pattern and single prominent pale blue nucleus, the picture being that of reticulum cell reticulosis. A few days later he began to deteriorate rapidly, ecchymoses appearing in the vicinity of the enlarged glands, and liver and spleen enlarging progressively. He became rapidly more anaemic in spite of blood transfusions and died suddenly on June 5, 1958, nearly 18 months after the onset of his first symptoms.

NECROPSY. This was performed 24 hours after death. The body was that of a fat boy with the moon-facies of cortisone overdosage, showing massive ecchymosis of the left arm and lower abdominal wall, and numerous small bruises scattered over the rest of the body. There was general enlargement of lymph glands, the tracheo-bronchial, mediastinal and pre-aortic abdominal glands being dark red in colour and soft. Petechiae were present on the surface of the heart (which was otherwise normal) on the pleura, and in the gastric mucosa. Fresh blood was present in the small intestine, which appeared normal in other respects. The liver was of

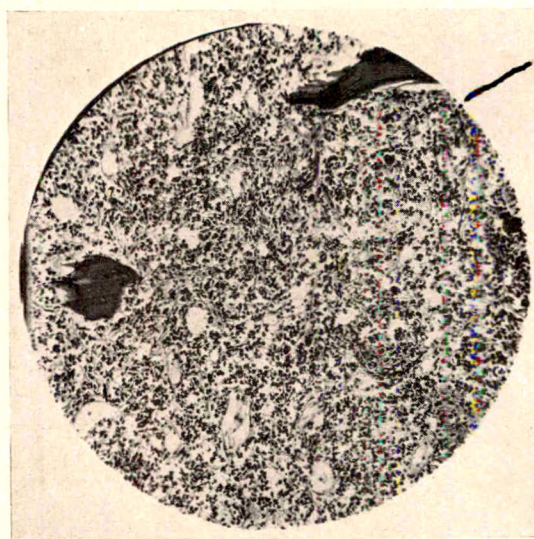


FIG. 10.—Bone marrow showing diffuse infiltration. (H. and E. $\times 90$.)

average size (870 g.) and was pale. The spleen was enlarged (180 g.) and deeply congested; other organs appeared normal. The cortex of all vertebral bodies and of the long bones was extremely thin and the marrow was dark red and prolific.

HISTOLOGY. Sections of spleen, lymph nodes and bone marrow (Fig. 10) showed replacement of the normal tissue by sheets of pleomorphic reticulum cells. The liver showed subcapsular and portal tract proliferation of these abnormal cells (Fig. 11), but the changes

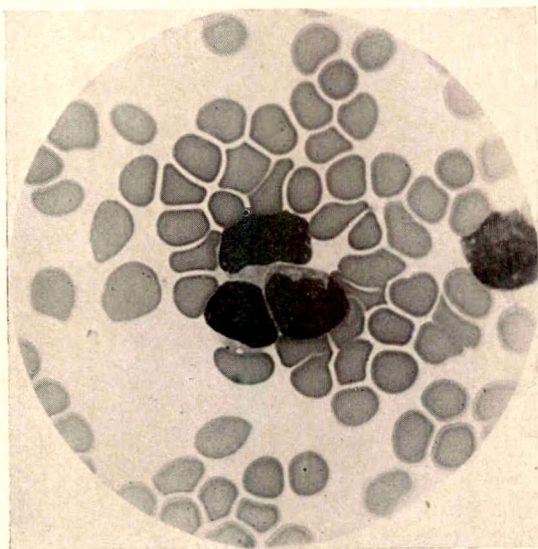


FIG. 9.—Bone marrow showing reticulum cells. ($\times 915$.)

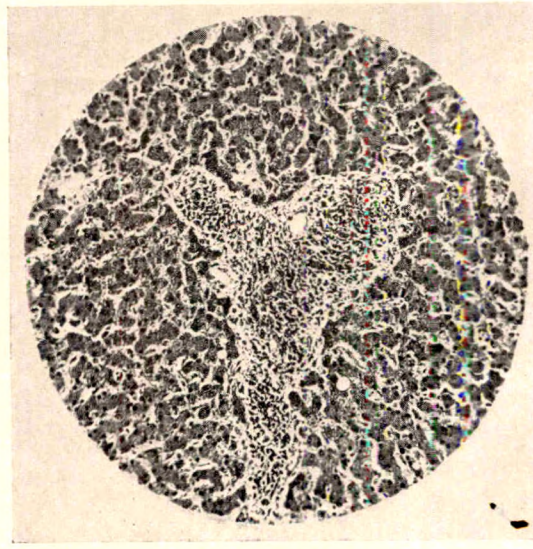


FIG. 11.—Liver showing infiltration of portal tracts. (H. and E. $\times 90$.)

were not intense. There was no evidence of lipoid storage. The infiltrating cells varied in size and shape, some being rounded, some polygonal and others elongated. Mitoses were scanty, reticulum production slight, but the cells stained with metallic stain and some showed evidence of erythrophagocytosis.

Discussion

Diagnosis undoubtedly depends on the histological interpretation of the type of abnormal cell seen in the marrow biopsy and necropsy sections. Cases of the type just described have been published under various names, but the unifying feature is a diffuse infiltration of the marrow by cells of reticulo-endothelial type. The two cases under discussion fulfil the clinical criteria advanced by Siwe, but at the same time show certain points of dissimilarity.

Case 1 had marked exophthalmos and foam cells in the marrow biopsy, but the classical triad of the Hand-Schüller-Christian syndrome was lacking. The rapid course of the disease in this case was characteristic of Letterer-Siwe syndrome, though the biopsy picture was more suggestive of the term acute xanthomatous reticuloendotheliosis.

Case 2 conformed more closely to the conception of a malignant reticuloendotheliosis, which was probably what the original authors described as Letterer-Siwe disease, but which in his case was checked over long periods by steroid therapy.

These two cases support a contention made by Lynch, Bain, Stanyon and Crang (1954) that two different disease entities are often confused under this eponym. That steroids influence all varieties of reticulosis there is no doubt; but the possibility of spontaneous remission must not be forgotten. The response to steroids accentuates neither the relationship nor the diversity of the pathological forms.

Summary

Two cases of reticuloendotheliosis of Letterer-Siwe type are described, and the effects of prolonged steroid therapy indicated. A brief review of the literature in relation to steroid therapy of the reticuloses is included.

I am greatly indebted to Dr. J. L. Hamilton-Paterson who performed the autopsies and supplied the pathological reports, to Dr. R. Bodley Scott who saw Case 2 in consultation, and to Miss M. H. Shaw for the photographs.

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A CASE OF SEVERE HYPERCALCAEMIA OF INFANCY WITH AN ACCOUNT OF THE NEUROPATHOLOGICAL FINDINGS

BY

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Hypercalcaemia of infancy has been divided into severe and simple or benign forms, each with distinct clinical pictures. However, Joseph and Parrott (1958) considered that the two forms were different degrees of severity of the same disease. Forfar, Tompsett and Forshall (1959) thought that the severe form, which tends to be recognized later in infancy, was the result of delay in diagnosis.

The severe form, which according to Fellers and Schwartz (1958) is 14 times less common than the simple form, was first described by Fanconi, Girardet, Schlesinger, Butler and Black (1952). Amongst its multiple symptoms and signs are dwarfism, mental retardation, persistent hypercalcaemia, hypercholesterolaemia, osteosclerosis and evidence of renal disturbance with albuminuria and nitrogen retention. The prognosis is poor. By contrast, the simple form first described by Lightwood (1952) is unassociated with mental deficiency and osteosclerosis and has a good prognosis.

Several workers have described the visceral changes, particularly renal, in severe hypercalcaemia, but neuropathological findings have not been hitherto reported. The object of this communication is to record a case which came to autopsy and had a full pathological examination.

Case History

The patient, the first born of healthy parents, the mother 18 and the father 37 years of age, with no family history of mental or neurological illness, was delivered normally after a labour lasting 44 hours. The pregnancy was normal. He weighed 9 lb. 6 oz. (4,220 g.) at birth and his head circumference of $14\frac{1}{2}$ in. (36.8 cm.) was of normal size. He had a capillary-cavernous 'strawberry' naevus on the outer side of the right elbow $\frac{3}{4}$ in. (2.2 cm.) in diameter and a similar lesion $\frac{5}{8}$ in. (1.6 cm.) in the left deltoid region.

At first he progressed normally but on the 3rd day he had a cyanotic attack and was given oxygen. Later the same day he had several tonic convulsions with

opisthotonus and flexion of all limbs, each attack lasting about two minutes. Cerebrospinal fluid was clear and xanthochromic with a protein content of 300 mg. % and a normal cell count.

He was weaned on to half-cream national dried milk at 17 days and changed gradually to full-cream milk at 12 weeks. One teaspoonful of cod liver oil was given daily. He was a slow feeder, often vomited and was constipated. These features persisted throughout life.

The cutaneous naevi increased in size up to the 4th month after which they became stationary. At this time his head circumference, $15\frac{7}{8}$ in. (40.2 cm.), was within normal limits. At 5 months his blood pressure was 124/76 mm. Hg and radiography showed normal bone development and calcification of hands and feet. Convulsions, consisting of sudden jumps, stiffness of the arms and legs, and cyanosis continued. Although some measure of control was achieved by sedation he sometimes had several attacks a day. At 9 months he was considered to be mentally retarded, deaf and blind with optic atrophy.

While in hospital from 11 months to 2 years and 3 months weight gain was satisfactory in spite of feeding difficulties and intercurrent respiratory infections. The fontanelles closed normally but his head size increased very slowly and at 2 years the circumference was $16\frac{3}{4}$ in. (42.6 cm.). His pupils did not react to light and he had slight nystagmus. The discs were small and pale but the retinae were normal. All limbs were hypertonic and the reflexes brisk. Plantar reflexes were extensor. The Mantoux 1/1,000 and toxoplasmin skin tests were negative. Marrow and blood counts were normal.

Many chemical investigations were carried out during the first 2 years of life. The blood urea was raised between 60 and 82 mg. %. Calcium in the blood varied from 11.3 to 16.6 mg. % (the diagnostic level given by Stapleton and Evans (1955) was 12.5 mg./100 ml.). Blood phosphates were between 5.5 and 9.9 mg. %; plasma protein 7.0 to 7.3 mg. %; serum cholesterol 293 mg. %. The alkaline phosphatase in six estimations varied between 15.7 and 28.4 King Armstrong units/100 ml. but there was a seventh estimation in which it was 5.4 units/100 ml. The CO₂ combining power was 30.8 mEq./litre. The I¹³¹ excretion test was normal.



FIG. 1.—Rounded face with eyes set wide apart, epicanthic folds and large low-set ears.

Paper chromatography revealed a normal amino-acid urinary excretion. C.S.F. protein returned to normal towards the end of the first year.

He was admitted to the Fountain Hospital at the age of 2 years and 3 months when he was found to be an idiot behaving like a 2-month-old baby, requiring three-hourly bottle feeding. He could not talk, sit, stand, walk, nor even lift his head. He showed no apparent interest in his surroundings and rapport could not be established. His weight was 22 lb. and head circumference $16\frac{3}{4}$ in. (42.4 cm.) (normal is 49.7 cm.).



FIG. 2.—Two small foci of calcification in the first premolar.

His face was round with eyes set wide apart, epicanthic folds were present and the ears were large and low-set (Fig. 1). He lay in a curious 'frog' position, the legs abducted at the hips and maintained rigidly in a flexed position. There was spastic diplegia.

Two weeks after admission to the Fountain Hospital, he developed a pyrexial attack (103 to 105° F.) with haemoconcentration and a leucocytosis of 20,000. Choreic movements of the face and limbs, head retraction and arching of the back occurred. Excitement and screaming attacks were frequently present and he often slept during the day and was sleepless at night. When asleep his movements ceased. The cause of his illness, which persisted intermittently till death seven months later, was obscure, in spite of many investigations. These excluded meningitis, middle-ear disease and other infections. A moderate degree of papillitis lasting about six weeks was noted. C.S.F. protein increased to 90 mg. % with a slight increase of globulin but other constituents were normal. Dr. Frank Elliott suggested that the cause of these symptoms and signs might be naevoid amentia with naevoid malformation at the base of the hypothalamus and pons, a diagnosis of some significance in view of subsequent findings. Radiography of the skull and spine at 2 years and 5 months revealed generalized osteosclerosis and two foci of calcification in the pulp of a deciduous premolar (Fig. 2).

He died from broncho-pneumonia at the age of 2 years and 10 months.

When the child was 10 months old the parents had a second infant, a girl, who developed normally and at 8 years was fit and well.

Pathological Findings. At necropsy performed on the day of death, the body was found to be well nourished. However, comparison with Coppoletta and Wolbach's (1933) tables of organ weights of infants and children revealed that his stature of 81 cm. (normal 88 cm.) was stunted and the weights of his heart, lungs, spleen, liver, kidneys and brain were all lighter than the average for his age. His head circumference was 42.6 cm. (normal 50.4 cm., S.D. = ± 1.35 cm.). He was therefore microcephalic.

Foetal lobulation was present in both kidneys (left 35 g., normal 49 g.; right 30 g., normal 48 g.), each of which showed longitudinal yellowish streaking of the medulla. Atheromatous deposits encircled the commencement of the aorta. The heart was well formed.

The brain, symmetrical in shape and covered by clear leptomeninges, weighed 825 g. (normal 1,140 g.). It was very soft at the time of removal and, with convolucional flattening, was considered to be oedematous. The olfactory and optic nerves appeared small but other cranial nerves were normal. Attached to the caudal part of the optic chiasma and anterior part of the tuber cinereum and chiasma and the hypophysis cerebri, was a soft grey nodule 4 mm. in diameter (Fig. 3). Basal vessels were normal. There were no naked eye abnormalities of the spinal cord.

Histological Findings. Coronal sections of the frontal, temporal and occipital lobes, the basal ganglia, mid-

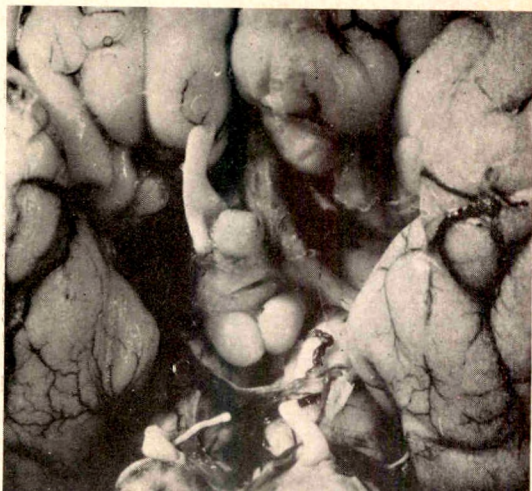


FIG. 3.—The small rounded infundibuloma arising from the floor of the third ventricle and anterior part of the hypophysis cerebri.

brain, pons, medulla, cerebellum, cervical, thoracic and lumbar cord were embedded in celloidin and sections stained by the usual neuropathological procedures—Nissl, Heidenhain, H.V.G., Mallory's P.T.A.H. and

Holzer techniques. Paraffin embedding was carried out on the optic nerves, cortex and viscera and sections were stained by the H.V.G., H. and E., P.T.A.H., Glees, Marsland and Loyez methods. Frozen sections of the cortex were used for Holzer, von Kossa and Scarlet R. methods.

The gyri were well formed but lamination within their grey matter was often indistinct and there was a generalized sparsity of nerve cells especially in layer III. Betz cells, looked for in many blocks, were absent from the motor cortex. The striate cortex could not be identified with certainty. Perigyril gliosis was increased in some areas, notably in the frontal, parietal and occipital lobes. The white matter was well medullated. However, it contained many ectopic nerve cells e.g. in the corona radiata there were five times more nerve cells than in an equivalent area of the brain of a mature newborn infant and 30 times more cells than in the brain of an infant of 1 year.

Apart from focal increases in Bergmann's cells, the cerebellum was well formed.

The nodule behind the chiasma was formed of glial cells and capillaries (Fig. 4). Most of the glial cells had round or oval nuclei with well-defined nuclear membrane. The nuclei contained powdery particles and two or three larger chromatin nodules. A few cells were smaller and hyperchromatic. The cells were arranged rather loosely except near the blood vessels where they were

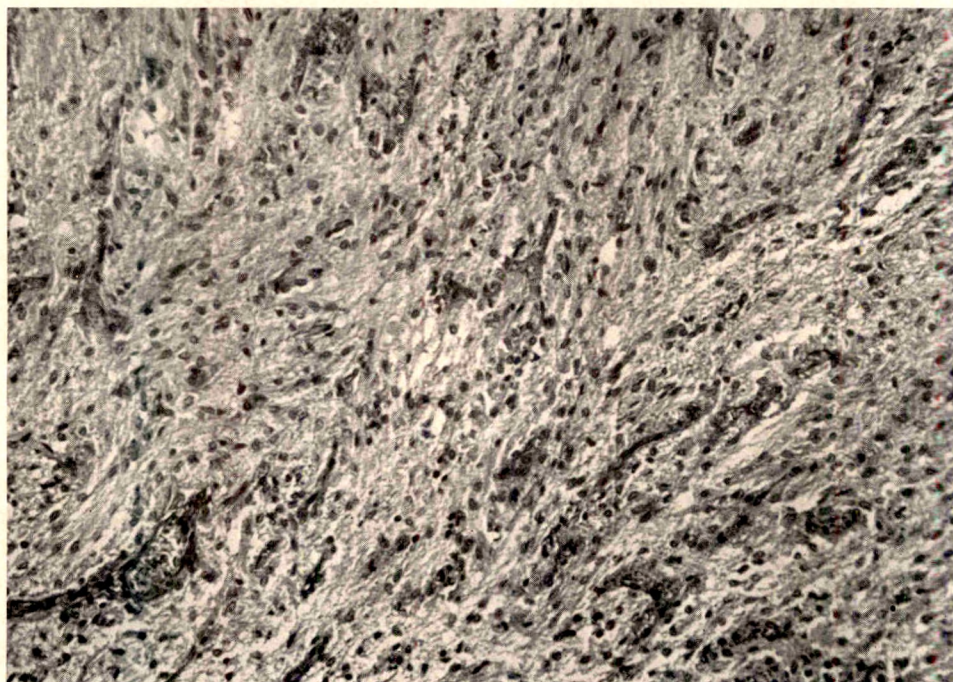


FIG. 4.—Rather haphazard arrangement of glial cells in the infundibuloma had a tendency to more compact arrangement around the vessels. (H. and E. $\times 156$.)

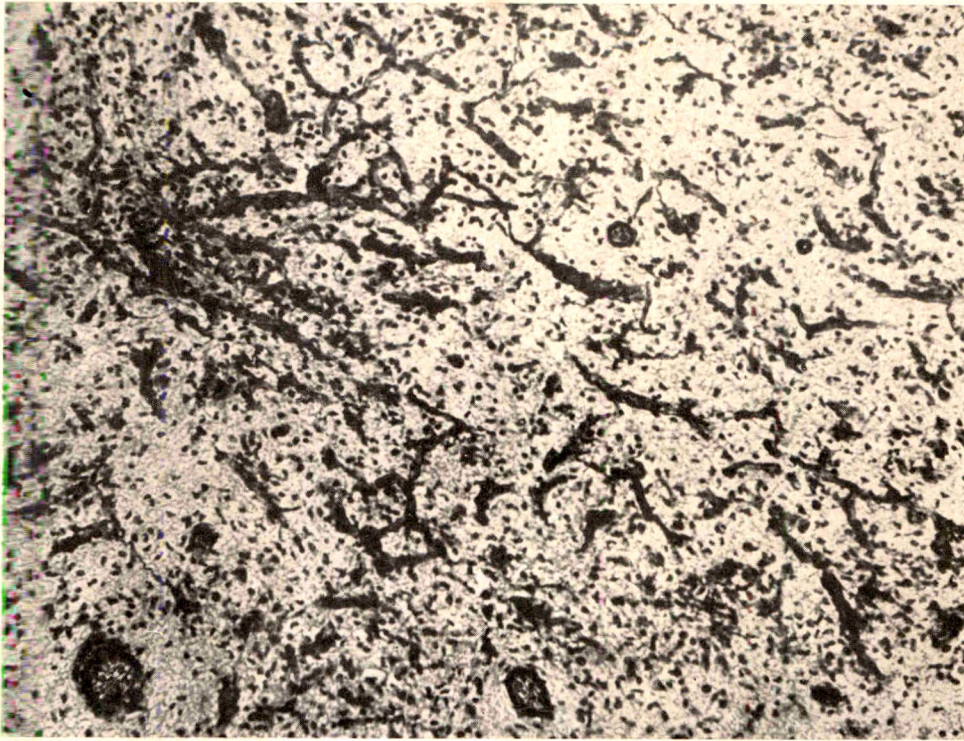


FIG. 5.—Collagenized capillaries, most of them bloodless, and inter-capillary gliosis in the cortical naevus (H.V.G. $\times 162$.)

denser. Their fine fibrils formed a delicate open network with occasional microcysts in the H. and E. and H.V.G. preparations. In the Holzer sections there were a few thick sturdy looking angulated fibres. Blood vessels were looped into several coils and contained an excess of reticulin in their walls. This gave them a bizarre glomerular-like appearance. There were neither multinucleated giant cells nor mitotic figures. A few globoid eosinophilic colloidal bodies or droplets were present.

A vascular naevus was found in the grey matter of the parietal lobe in the vicinity of the Rolandic fissure when this was sectioned. Situated in the grey matter bordering a sulcus, it measured approximately 1.5 mm. in length and involved layers I, II and III (molecular, external granular and pyramidal cell layers). It consisted of a network of collagenized capillaries (Fig. 5). Only a few of the capillaries contained red cells. Elastic tissue was not seen in their walls. Glial cells were numerous throughout the area. A dense feltwork of glial fibres was arranged in a racemose fashion around the periphery of the lesion, from which many branches invaded neighbouring grey matter. There were neither saccular nor fusiform dilatations. Calcification was absent.

Numerous calcareous deposits were situated chiefly in the outer half of the pyramids of the kidneys with occasional foci in the medullary rays. Interstitial fibrosis was present around these foci and ischaemic

changes were seen in some glomerular tufts. It was often difficult to identify the precise site of the calcified structures because of distortion by fibrosis. Many were large enough to be seen by the naked eye (like grains of black pepper in the von Kossa preparation); for instance, some of the larger deposits were contained within a thin lining of fibrous tissue and it was impossible to say whether they originated within the lumen of a tubule, in its epithelium or in the interstitial tissue. These large deposits compressed surrounding tubules. The smaller deposits were also difficult to place, but some appeared to have formed below the level of the tubular epithelium which they had dislodged towards the lumen. Many smaller deposits appeared to be interstitial.

Glomerular changes were focal and included shrinkage of the capillary tufts with hyperchromasia of nuclei. Fibrous tissue was increased around some Bowman's capsules and the interstitial tissue contained an excess of fibrocytes and round cells. There were no polymorphonuclear cells; there was no calcium-like deposit in the glomeruli or adjacent tissue and blood vessels were normal.

The available sections of the pituitary gland were small when compared with a gland from a child of similar age. Apart from congestion of the sinusoids it appeared normal structurally. Atrophic changes were conspicuous in the thymus and included smallness of lobules with

poor differentiation between cortex and medulla; Hassall's bodies were calcified and there was a great deal of fibrous stroma and fatty infiltration. There was infiltration of the portal tracts by small round cells. Broncho-pneumonic changes were confirmed in the lungs. Other viscera appeared normal.

Discussion

The hypercalcaemia and the clinical features of mental deficiency, osteosclerosis and stunting made it reasonably certain that this boy suffered from a severe form of hypercalcaemia of infancy. Failure of the skull to grow adequately after birth and the development of osteosclerosis signified the progressive nature of the disease. Nephrocalcinosis, found in both forms of this disease, was also present and the renal lesions were similar to those described by Dawson, Craig and Perera (1954), Rhaney and Mitchell (1956), and Shanks and MacDonald (1959) Type III lesion. An unusual feature was foci of metastatic calcification in the pulp of a deciduous premolar. Dawson *et al.* (1954) found similar lesions in a lower deciduous incisor.

Micrencephaly, poor lamination of nerve cells and universal paucity of nerve cells in the grey matter especially in layer III (pyramidal cell layer) were severe enough to account for the mental deficiency in this boy. The paucity of cortical nerve cells could probably in part be due to the excessive number of ectopic nerve cells in the white matter indicating a failure in the normal migration of neuroblasts towards the pallium, either in the later months of pregnancy or early in infancy. Clearly, with the early onset of convulsions and initially raised cerebrospinal fluid protein there was evidence that the disturbance of the nervous system was already present in early infancy. It is also impossible to exclude the possibility of ictal neural damage.

Rhaney and Mitchell (1956) reported medial calcification of the middle cerebral artery within the basal ganglia in a child of 10 months whose brain weight was normal and who suffered from the mild form of the disease. The vessels in this child were free from this abnormality.

The tumour situated between the optic chiasma and hypophysis cerebri had many of the features of an infundibuloma; a condition recently reviewed by Wolman (1959). Its situation invites speculation into the effects it may have had on the child's metabolism and physical state. As indicated in the history, a lesion of the hypothalamus was suspected in life. Diabetes insipidus was not present. Although he was well nourished, he was not excessively fat and his genital organs were quite

well developed, there being thus no signs of adiposogenital syndrome. As a matter of interest and by contrast, Kagan (1958) described a large tumour of the third ventricle, regarded as an astrocytoma, in a 5½-month-old infant in whom the blood calcium was normal and the main features were anorexia and inanition.

The histological character of the vascular naevus did not fit easily into Russell and Rubinstein's (1959) classification of capillary telangiectasis, cavernous angiomas and venous and arteriovenous angiomas. It resembled most a racemose venous naevus composed of small channels. However, a pia-arachnoid component was not demonstrated and the lesion in this child was within the substance of the brain. Corrin (1959) stated that cavernous angiomas were similar in structure to the common cutaneous angiomas and that occasionally they were associated with angiomatous lesions of the skin and other organs. Unfortunately, the skin lesions were not examined histologically.

It was impossible to decide whether the hypercalcaemia was causally related to the naevoid anomalies and the infundibuloma or was a fortuitous complication such as might have arisen from some fault in the early feeding involving calcium and vitamin D or hypersensitivity to vitamin D; causal factors which have recently been discussed by Bonham Carter, Dent, Fowler and Harper (1955), Morgan, Mitchell, Stowers and Thomson (1956), Fellers and Schwartz (1958), and Forfar *et al.* (1959). Nevertheless, it could not be ruled out that the more economical explanation of a single cause such as a biochemical defect manifested itself as localized faults of morphogenesis.

Summary

An epileptic microcephalic idiot boy was stunted and had spastic quadriplegia, capillary-cavernous naevi of the skin and hypercalcaemia and osteosclerosis of the skull. Pathologically, there were micrencephaly, generalized paucity of nerve cells in the grey matter and an excessive number of ectopic nerve cells in the white matter, a gliosed vascular tumour of the left cerebral cortex and an infundibuloma.

Our thanks are due to several colleagues at the Fountain Hospital and the Postgraduate Medical School who supplied information.

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BOOK REVIEWS

Atrial Septal Defect. By H. GÖSTA DAVIDSEN. (Pp. 225; 347 refs; 49 figs; 12 tables. D. kroner 50.00.) Copenhagen: Munksgaard. 1960.

Accurate information concerning the natural history of disease is as elusive as it is important, for without this knowledge rational treatment can hardly be said to exist. In attempting to set down the story of atrial septal defect Dr. Davidsen has clarified the background against which the treatment of this anomaly must be set. Although most of the 225 paper-backed pages are taken up with the minutiae of a thorough, careful and painstaking study of 15% of the atrial septal defects in Denmark, being a series of 132 patients seen at the Rigshospitalet, Copenhagen, considerable space is devoted to an analysis of the 190 autopsy reports in the literature. These latter records are admittedly unrepresentative, but they are unique, as they antedate the era of operative treatment and from them the author has extracted an amazing amount of information. In 68 of the 132 patients of Copenhagen the diagnosis of heart disease was made before the age of 7 years. The subject is presented well in eight chapters with excellent summaries of each. From the gravity of the late prognosis in atrial septal defect, the author concludes that there are sufficient grounds for attempting an improvement in the prognosis by surgical treatment. Such treatment should be carried out before irreversible changes have occurred in the pulmonary vessels and cardiac valves. The scope of the book excludes the technique or results of operative treatment. In a chapter devoted to electrocardiographic changes some reference might have been made to the value of the vector cardiogram. The reproduction of radiographs is good, and the diagrams and line drawings prepared by the author himself are commendable. Full references are given to the 347 publications quoted and the index is accurate if a trifle curtailed. Spelling mistakes are few for a book published in a language 'foreign' to author and printer, and the quality of print and paper is good.

The Purpose and Practice of Medicine. By SIR JAMES SPENCE. (Pp. x + 308; illustrated. 42s.) London: Oxford University Press. 1960.

This book is made up of a selection of 20 of the papers and lectures of James Spence, edited anonymously by his friends and colleagues. They are divided into sections entitled 'The Nature of Disease', 'The Study of Disease', 'Children and Families', 'The Care of the Child', and 'The Practice of Medicine' and the 'Training of Doctors'. The first of these sections shows the young Spence writing papers on pernicious anaemia, xerophthalmia, epituberculosis and other medical subjects of current interest in the era 1920-1933. These probably

differ little from similar papers written by others at the time, but in 1934 there was published an 'Investigation into the Health and Nutrition of Certain of the Children of Newcastle upon Tyne between the Ages of 1 and 5 Years'. This work, done at the time of the great depression, marked the beginning of Spence's long and fruitful collaboration with the Health Authority of his own city, which led on to the unique 1,000 family survey, launched before his death and carried on afterwards by his collaborators. From this time, as his bibliography shows, he became less interested in clinical medicine itself, in so far as it concerns itself with particular diseases, and more and more interested in the way in which medicine should be studied and should be taught.

In turn this led on to the main concern of the latter years of his life, the institutions which men create to fulfil particular needs, and the manner in which these institutions evolve, or fail to evolve, as those needs change. He liked to regard the human family as the oldest of its institutions, and his masterly discourse on 'The Purpose of the Family' should be read in this context. His membership of the University Grants Committee brought him into close contact with the university and the teaching hospital *qua* institutions, and during the last decade of his life his interest, his talk and his energies were increasingly taken up with university policy. Unfortunately he wrote little on this subject.

The book ends with his address to the Newcastle and Northern Counties Medical Society, given a few months before his death in 1954. He spoke on Institutional Medicine, and the opening words are beautifully characteristic of his style.

"It is, I think, one of the inherent peculiarities of an Englishman, and more particularly of a Northumbrian, that, if you scratch him he begins to brood over his institutions. And then from time to time he reforms them. He is, as it were, still in those tremendous years before and after 1688, when our revolution was settled more by sincerity of argument than by force of arms, and when there were men of the calibre of Halifax the Trimmer to hold the balance. Now, again, in this century we are in the midst of another revolution, which is shown in our concern about our institutions. If we have neither the vigour, which is an affair of the spirit, nor the means, which is an affair of the intelligence, to reform our institutions, it will be a matter of interest mainly to the historians of the future; but such a state of affairs will be cold comfort to those of us who believe that the excellence of a civilization is shown in the capacity of its citizens constantly to reform its institutions in order to meet its changing cultural needs. But change may be for the better or the worse, and in remembering this we should be guided by Burke's admonition, that "merely to innovate is not to reform".

The style of his prepared utterances is terse, witty and embellished with apt references to the work and words of men, past and present, whom he admired. Discussion of the present and future is characteristically based on experience to be gained from a study of history,

for his historical sense was one of his outstanding intellectual qualities. Alas, his prepared speeches, vivid though they are to read, cannot give more than a faint impression of the unforgettable delight of his conversation, nor of the effect of his extempore contributions at conference or committee. Yet it was by these means that he mainly achieved the great influence he had on his contemporaries during his lifetime. His approach to life had much of the imaginativeness of the artist about it, so that his judgments seemed to be arrived at intuitively, and his opinions often enough had a touch of waywardness about them, leading to his being apt to take an entirely unexpected line on some controversial issue. Inevitably these aspects of his personality cannot be reflected in a book made up of his formal utterances.

Yet happily, something of the charm of his personality, of the enchantment of his companionship, and of the impact which these made upon those who knew him is brought out in the excellent Memoir (in effect a short biography) which Sir John Charles has written for this book.

All must be grateful to those who have given us this book, for James Spence was one of the two or three men whose ideas have shaped paediatrics in this country since the War.

Cancer and Allied Diseases of Infancy and Childhood. Ed. I. M. ARIEL and G. T. PACK. (Pp. xiii + 605; 344 figs. London: Churchill. 1960.)

This is a work of multiple authorship in which 27 contributors, all from the United States, have cooperated. The editors state that it is 'the first comprehensive treatise devoted exclusively to the clinical aspects of cancer and allied diseases in children'. The list of contributors includes names that are well known outside the United States and all are workers of experience and authority.

The scope of the book is wide. Nearly every possible type of neoplasm that may afflict children is mentioned. A liberal interpretation is given to the term 'allied diseases', a number of developmental anomalies being included which are allied to cancer only as possible problems in differential diagnosis. The principal interest of the book is surgical, although chapters are devoted to leukaemia and the 'reticuloendothelioses', which are mainly of medical interest. Some of the authors describe surgical techniques and many give details of radiotherapy. An interesting feature of many contributions is the evaluation of results of treatment culled from large series of cases in various important centres. Pathology is introduced only for the purpose of classification and to indicate the bearing of histological structure on the behaviour of tumours and consequently on treatment. No detailed pathological descriptions are given.

A few criticisms may be offered on pathological grounds. The controversial 'Ewing's tumour of bone' is accepted as a pathological entity and the frequency with which the syndrome is produced by secondary neuroblastoma is ignored. In Chapter 13 the author's attempt to resolve the existing terminological confusion

between dermoid cysts and teratomata leaves the reader still confused. It is obvious that the term 'dermoid' is too widely applied. A new confusion is created by applying the term 'non-lipid reticuloendotheliosis' to Hand-Schüller-Christian disease in contrast to the diseases of Gaucher and Niemann-Pick, which are termed 'lipid reticuloendotheliosis'. This terminology is unfortunate because Hand-Schüller-Christian disease has hitherto been known as lipid reticuloendotheliosis and Letterer-Siwe disease as non-lipid reticuloendotheliosis.

It is surprising that the treatment of neuroblastoma with vitamin B₁₂ is dismissed in two brief sentences. In view of the encouraging results reported from Great Ormond Street Hospital, this merits more detailed consideration in a comprehensive book such as this.

The editing is good and little overlapping between contributors has been permitted. A few misprints and grammatical errors have escaped correction. The book is well produced and generously illustrated, especially with clinical photographs and radiographs. A copious bibliography is provided. The index is full but would be improved by the use of heavy type to indicate principal references among multiple entries.

The Development of the Infant and Young Child—Normal and Abnormal. By R. S. ILLINGWORTH. (Pp. 318; illustrated. 27s. 6d.) Edinburgh and London: Livingstone. 1960.

This is a book about the mental development of children during the first five years of life. It is not concerned with physical growth nor does it trace the mental development in specific mental diseases. The title of the book could mislead the casual reader and has rather a dull, prosaic sound about it. Not so the text. In articles published in recent years Professor Illingworth has shown great skill in portraying the social and intellectual development of young children in words readily comprehensible to paediatricians, general practitioners and lay social workers alike. In this book he has excelled himself. This is a splendid simplification and condensation of the original studies of Gesell and others adapted by the author for day-to-day clinical use and widely modified by his own large experience in paediatric practice. The reader is usually given a clear expression of opinion and many illustrative case histories are recorded. There is a wealth of good, sound, practical advice and the text includes several specimen charts for recording developmental progress which can be applied without any specialized equipment or training. There is wise emphasis upon the value of personal history-taking by an experienced clinician, though not everyone would draw quite the same conclusions from the examples quoted. There is, perhaps necessarily, a good deal of repetition in the early chapters where norms of development are discussed in the text, then classified in tables by age and then again grouped in more complex tables. The perpetual problem of deciding what is 'normal' and when behaviour becomes 'abnormal' has often been ingeniously circumvented in this book by the device of having three standards: (1) Normal, (2) Variations from Normal; (3) Abnormal.

Each chapter has an excellent bibliography and the book has a good index. It would be surprising to find no mention of autism in the index, though it receives passing mention in the text, but for the conviction that the author is really concerned with normal development and only considers abnormalities in order to illustrate how normal development can be distorted.

Chapters 5 and 12 deal with pathological development in a general fashion rather than in specific disease entities. There is a short chapter on the diagnosis of cerebral palsy and an entertaining, if not very instructive, chapter on persons of exceptional mental superiority.

The illustrations are clear and useful adjuncts to the text and there are very few misprints. There is a slight error on page 251 where two lines on electro-encephalography are allowed to intrude into discussion of pneumo-encephalography and, taken in conjunction with the following sentence, might suggest that electro-encephalography is a dangerous test.

This book is entertaining and it is practical; it is very well written; it should certainly be read by all who are engaged in the study of young children and it should be purchased for permanent reference rather than borrowed from a library.

The Physiology of the Newborn Infant. By CLEMENT A. SMITH. (Pp. xii + 497; 62 figs. 95s.) Oxford: Blackwell Scientific Publications. 3rd edition. 1960.

The supremely high standard of previous editions of this classic study are more than fully maintained. Many chapters have been re-written. Revision has involved careful appraisal of advances made in the study of neonatal physiology since publication of the previous edition. Acknowledgements make special reference to the activities of the Nuffield Institute for Medical Research at Oxford, and the Department of Experimental Medicine at Cambridge. The format of the book remains unchanged. Each chapter consists of a scholarly evaluation of the present state of existing knowledge and prevailing views, and concludes with a summary outlining the significance and practical application of that knowledge in the clinical care of the newborn infant. Together, the richness of his personal research contributions and the wide ranging wealth of his references afford some indication of the immensity of the task undertaken by the author. With admirable skill, he marshals his evidence; from a maze of often conflicting views delineates a clearly defined theme; and with carefully developed, logical argument arrives at his assessment of the present position. Established facts are given as such. Theories as yet unproven are presented in unprejudiced form, but with an indication as to the extent to which they may be legitimately permitted to influence clinical practice. Herein is to be found one of the especial among innumerable attractions of the book to practising paediatricians. Seldom is accumulated experience and erudition available in such stimulating and readable form, as in this book. Could there be more penetrating answer to the question 'Does physiologic jaundice ever cause kernicterus, or other significant pathology?' than the author's—'The clinical

problem of physiologic jaundice has heretofore been essentially a problem of differential diagnosis. It may now have become one of definition'?

Diseases of the Nervous System in Infancy, Childhood and Adolescence. 4th ed. By FRANK R. FORD. (Pp. xvi + 1548; 215 figs. 236s.) Oxford: Blackwell Scientific Publications. 1960.

Frank Ford's textbook, which is one of the major classics of medicine, has now reached its fourth edition. The first appeared in 1937. It is becoming increasingly rare for a single writer to attempt to cope with such an extensive field, but the result certainly has advantages in respect of uniformity of presentation and simplicity of reference. Dr. Ford's approach is refreshingly personal, thus: 'Hysterical deafness is described but I have never seen it.' In this way he avoids carrying over material of doubtful validity from previous texts. At the same time his account of the subject is very extensive and authoritative. There is no other work with which it can be compared and it is essential to any library dealing with paediatrics, neurology or child psychiatry.

The price of the book makes it unlikely to appeal to the individual purchaser though it is worth much more than a great deal of ephemeral literature. The volume is well documented and some idea of the scope can be gained from the fact that the index occupies 221 pages. The index would have been much more convenient if authors and subjects had been listed separately. The mere weight of the book makes it cumbersome for the less athletic reader; perhaps two volumes should be considered if it is to grow any more.

Dr. Ford does not give an account of the neurology of old age, but otherwise his text is so full that one wonders in what other respect it differs from a comprehensive treatise on neurology. None the less it will continue to make a special appeal to those interested in children. The revision of the new edition appears very adequate and has obviously involved critical scrutiny of recent publications. Crome's work on the neuropathology of mental subnormality is mentioned four times and a bibliography is provided in addition to references in the text. The illustrations are excellent and the quality of the paper does full justice to them.

In his section on tuberous sclerosis Dr. Ford states: 'No doubt tuberous sclerosis is frequently responsible for convulsions which are mistakenly attributed to epilepsy'. This might indicate a dualist approach, but in fact this is not reflected in the excellent chapter on epilepsy which fully recognizes the principle of causality and refers only in passing to the 'so-called essential epilepsies' as those in which 'no clinical evidence of organic disease of the brain can be found'. The author also shows a very proper scientific scepticism in regard to a special 'epileptic personality'.

It is rather surprising to find such an authority as Dr. Ford falling into the usual trap about 'mongolian spots' which he described as part of the syndrome of mongolism. Perhaps we could avoid these difficulties if we used the Russian term of 'Down's disease'! The true Mongol spot is a naevoid formation in the lumbo-sacral area,

found among Mongols and Tatars, and has nothing to do with the clinical condition of mongolism. The term 'Mongolian Idiocy' should certainly now be abandoned since, as Ford himself points out, most of these children are of imbecile level. Also, tuberculosis is no longer very common later in childhood among children with mongolism. This edition went to press too soon to record the interesting new developments in regard to chromosome constitution.

Dr. Ford has done a great service to neurology. His book is an essential work of reference in this and related fields. It will continue to be of great assistance to the practitioner, the teacher and the research worker. The English is lucid and simple.

Infant Foods and Feeding Practice. By HERMAN FREDERIC MEYER. (Pp. 360; 14 figs. 78s.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

This book, by a Chicago paediatrician, who is Associate Professor of Paediatrics at North-Western University Medical School, is most refreshing. Written by one with a long experience of routine well-baby care as well as hospital and domiciliary paediatric practice, it is the successor of 'Essentials of Infant Feeding for Physicians' which was well known in the United States a few years ago. In this volume the author has emphasized and amplified those sections of the original book which proved most popular and helpful, and the title of the book has been appropriately changed.

The theory and practice of dietetics in the first year of life including the newborn period, are thoroughly reviewed and discussed in a very satisfying, often humorous, down-to-earth manner by one who has clearly had a great deal of experience, not only with patients but also with parents, doctors and students.

Breast feeding and its present position in paediatric practice in the United States and many other countries are fully and objectively considered, though the management of the numerous minor breast disturbances which frequently arise in the puerperium, and often unnecessarily lead to weaning, has received too little attention. The author deplores the fact that in the United States only 2% of babies are now being breast fed on discharge from maternity hospital, but he is encouraged by a reversal of this regrettable trend in the better educated sections of the community, such as university graduates.

Artificial feeding has been reviewed from its evolutionary aspect leading to the contemporary swing back of the pendulum to more fundamental, simpler methods, and the somewhat confused American scene with its 73 varieties of artificial infant foods has been arranged and coordinated into a rational picture.

The various food elements, proteins, fats, carbohydrates, minerals and vitamins, are considered in their modern context and many points which are new in a book on infant feeding attract the reader.

The section on mixed feeding is also a happy blend of the modern scientific approach and practical wisdom and experience and it is gratifying to find that the author, like most of the leading American and British paediatricians,

sees no indication for introducing mixed feeding until the third or fourth month in the average infant, though it is rightly stressed that in this form of feeding, as in milk feeding, there are great individual variations.

The last chapter 'Clinical Trivia and Philosophic Observations in an Every-Day Feeding Practice' is an entertaining and intensely practical account of common misconceptions and minor problems. It will be particularly useful for students and young paediatricians and general practitioners in whose eyes some of these minor problems often loom large and may be very disturbing.

The 200 references will prove valuable for those who wish to pursue various points further. Although written for American paediatric practice this book will prove equally welcome and valuable in this and other English-speaking countries, for the basic principles of dietetics in infancy are similar everywhere.

Neue Paediatrische Urologie. By ERICH ZAPP. Beiheft zum Archiv fuer Kinderheilkunde, 40. Heft. (Pp. 142; illustrated.) Stuttgart: Ferdinand Enke Verlag. 1960.

In the foreword the author states that this little book is written for paediatricians in order to acquaint them with recent developments in paediatric urology. The main emphasis is on diagnosis; therapy and operations are only briefly mentioned.

The English reader will find this little monograph too short to be of much value to paediatricians; but it may be of some use to undergraduates and practitioners. It appears to be a little out of date; although written in 1960, many of the advances in paediatric urology during the last decade are not mentioned.

The first chapter contains brief descriptions of paediatric urology and diagnostic methods. It seems strange that x-ray cinematography and studies with the image intensifier, which have done so much to unravel some of the confusion surrounding paediatric urological conditions are not described at all, and that the micturating cysto-urethrogram, which is perhaps the most important of all radiological investigations in childhood, receives only scant mention.

Of the succeeding chapters, some, like the one on urinary infections and stone formation in the urinary tract, are very adequate, others, like the one on megaureters, ectopia vesicae, bladder neck obstruction and the neurogenic bladder, are somewhat out of date, especially when the treatment and indication for treatment are discussed.

It is, of course, difficult to compress such large and rapidly expanding subjects into a few pages, but it is not easy to understand why some extremely rare conditions like atresia of the urethra and congenital elephantiasis of the penis are described in some detail, and why some common lesions like phimosis and incompletely descended testicles are only very briefly mentioned.

The author has written a most readable and concise little monograph based on a comparatively small series of cases. The results mentioned in this book do not quite come up to those published by the larger Paediatric

Urological Centres in this country or the United States of America. One is therefore forced to agree with Doctor Zapp when he states that it is unfortunate that in Germany paediatric urology is not practised by specialists in this field, but remains an appendage to adult urology.

Intussusception in Infants and Children. By MARK M. RAVITCH. (Pp. 121; illustrated. 76s.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1959.

Intussusception is still a potential killer in young children, and anyone dealing regularly with this condition will find something of interest in Mark Ravitch's book. It is the first of a new series of paediatric surgical monographs, and is based on the author's experience at the Johns Hopkins Hospital, Baltimore.

The essential theme of the book is the treatment of intussusception by barium enema reduction. As soon as the diagnosis is made, an intravenous infusion is started. An ungreased 45 ml. Foley bag catheter is inserted into the rectum, the balloon is inflated, and the buttocks tightly strapped. The catheter is connected to a reservoir of barium at a height of 3-3½ ft. above the table. Thereafter, reduction is performed under fluoroscopic control. When the ileum is seen to fill freely, reduction is complete.

This technique in Ravitch's hands is curative in 70 to 75% of all cases. When reduction is incomplete (in 25 to 30%) it is completed by open operation through a McBurney incision, thus avoiding a centrally placed scar. Using this technique at the Johns Hopkins Hospital, in the 10 years from January 1948 to January 1958, there have been 52 cases, and no deaths. Incidentally, there were only two resections.

Ravitch is convinced, by his own experience and that of other clinics using this technique, that primary reduction by hydrostatic pressure is superior to and safer than open operation. Attention is drawn to the curious fact that the incidence of intussusception is much higher in Britain and Scandinavia than in the United States. There are only six to eight cases a year in Ravitch's clinic, contrasting with 30 to 40 cases a year in any big Children's Hospital in this country.

There is an excellent chapter on errors in diagnosis, leading to delay and even to death of the child. Common mistakes are misdiagnosing intussusception as dysentery, and preoccupation with an associated serious illness. This chapter contains much valuable information.

In the chapter on symptomatology and physical signs, the omission of 'pallor' is a curious one, since it is so common a feature.

There is a section on experimental studies on dogs, in whom intussusception was artificially induced. This

proves that the apex of the returning limb of the intussusception is the first to go gangrenous. This also shows that micro-organisms can be found on the serosal surface of the bowel in from four to 48 hours, and the more completely the blood supply is arrested, the more rapidly do they pass through the bowel wall. This underlines the importance of antibiotic therapy.

Resection procedures are discussed. Almost every manoeuvre has been tried at some time. Primary resection and anastomosis is still the treatment of choice and holds the field today, but in the extremely ill baby or with oedematous bowel of doubtful viability, there is a place for a decompressive resection of the Mikulicz type, coupled perhaps with anastomosis. Resections in any single clinic are so few that comparison of results is, in Ravitch's opinion, difficult.

Every clinic has experience of the child who arrives almost irretrievably moribund early in the disease. There is no full discussion in this book of that most important though still mysterious topic, the cause of death in this form of obstruction. There are no hints as to the possible aetiology of intussusception. This, too, remains a mystery.

The production as a whole is excellent, easy to read and profusely illustrated by first-class radiographic studies. There is a very full bibliography.

This book should be read by all those who are called upon to treat intussusception in childhood.

Kranke Sauglinge. Edited by C. H. VERBOOM. (Pp. xii + 367; 8 figs. D.M. 39.60.) Stuttgart: George Thieme. 1960.

As its title implies, this book deals with clinical conditions arising in infancy. There are 20 chapters, the lengthiest of which deal with illnesses in the newborn, congenital defects, feeding problems, vitamin deficiencies, infectious diseases and modern therapy. A chapter is devoted to tetany, infections of the cranial contents and acro-dynia. Other subjects dealt with include diseases of the respiratory, urinary, haemopoietic and integumentary systems and of the ear, nose, throat and eyes. Emphasis is on treatment, including prophylaxis considered against the background of health in infancy. Intended for the practitioner, the publication is essentially a reference book. It is based upon the combined experience of six clinicians who practise their different specialities at the Infant Clinic of the University of Freiburg i.Br. Sound material is presented in highly concentrated form. Illustrations number only eight and all relate to laboratory aids. There are no references but a selected bibliography is provided. The book is unlikely to appeal on any large scale to paediatricians or general practitioners in this country.

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